DIALOGUE
ONTARIO PSYCHIATRIC ASSOCIATION

NOVEMBER 2009

# President's Message

*Dr. Paul Mulzer*

It certainly has been a very eventful year to date. Members who were fortunate to attend our Fall Conference enjoyed an inspiring presentation by Nancy McWilliams, PhD. I extend my thanks to the Fall Conference committee members and their chairperson, Dr. Tina Chadda, for an excellent CME. Our efforts and attention are now keenly focused on our Annual Conference. I'd encourage your attendance at this historic provincial conference, marking 90 years of commitment to our profession and to the patients we serve. I look forward to meeting you when we assemble on April 23 & 24, 2010, in Toronto at the King Edward Hotel, for what promises to be an exceptional event. I'd also like to express my appreciation to Dr. John Deadman for his diligence as our archivist. You will certainly see the results of his tireless efforts in future publications and at our Spring Conference.

This summer has been a very productive time for the OPA as we responded to the Ontario Health Minister's 10-year plan for transforming mental health care and addiction services. The OPA and OMA psychiatry members attended the Summit on July 13 & 14, which sought to gather together key stakeholders to discuss the strategic plan that was, curiously, not released in advance of the meeting. I also attended the inter-ministerial committee, which was meeting in tandem with the government 'town hall' and to which I gave a detailed response to this discussion paper. I also submitted a formal response highlighting my key concerns. I did endorse the portions of the "Every Door is The Right Door" which I felt enhanced care provision. I strongly objected to its minimization of the critical importance of treatment. I also thought its blurring of the clinical line between 'life experiences', system navigators and formal therapy was unacceptable and required a clear rethink. We certainly agree that providers and those with "lived experience" have valuable roles to play but the scope of responsibilities and competencies needs to be clearly defined and not obscured.

I think it is telling that the Ministry is "transforming" the system. They are not oiling the mechanism or fine-tuning the apparatus. This is a proposed major overhaul of care delivery done with no new funding. In their discussion document they correctly note that $1 spent on mental health care and addiction saves $7 dollars in health cost, $30 in social expenses and lost productivity. This would certainly seem to be a very prudent capital investment. In fact, I could not think of a more effective stimulus

> *IT IS OUR DESIRE TO PROMOTE CHANGE THAT IS THOUGHTFUL, PROGRESSIVE AND SUSTAINABLE.*

expenditure. This glaring inconsistency is the key reason why many key providers we networked with during these forums viewed this process with a healthy dose of skepticism. Our challenge is to not have this well-intended initiative become yet another leather bound volume in the denial, wish and obscurity series.

Stigma is identified as a major barrier to engagement. Unfortunately they offer very few solutions. They do not appear prepared to invest in the aggressive public education campaign required to challenge fallacies and misconceptions. They also failed to acknowledge that psychiatrists share a stigma with our patients as care providers to the vulnerable and marginalized portion of the population. This document, at times, seems to perpetuate this provider stigma and its prevailing mythology with references such as "provider-centered care" and a need to be "proactive and not reactive". It also appears to reproach frontline staff for the silos in the system, many of which have been created by funding models that lead to

> *WE AGREE WITH THE MINISTER THAT THERE IS NO HEALTH CARE WITHOUT MENTAL HEALTH CARE.*

unnecessary duplication and redundancy. It also fails to appropriately acknowledge the many innovations in mental health care that have advanced service delivery. These critical initiates have often been lead by psychiatrists.

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| *OPA Office* | Ontario Psychiatric Association<br>2233 Argentia Road, Suite 100<br>Mississauga, ON L5N 2X7<br>Tel.: 905-813-0105<br>Fax: 905-826-4873<br>opa@eopa.ca<br>www.eopa.ca |
| *Publisher* | Dr. Paul Mulzer |
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## Contents



## From the Editor

THE OPA started its fall season on a high note with the Psychotherapy Section's very successful Fall Conference. OPA members and guests experienced an outstanding presentation by our guest speaker – Dr. Nancy McWilliams. Congratulations to Dr. Tina Chadda and her committee for organizing such an excellent event! Please see our photos from the Conference on the central spread of this issue.

The 2010 Annual Conference is fast approaching, and if you are interested in submitting an abstract, please refer to the guidelines on page 3.

In this issue of *Dialogue* you will find much that is new and informative. We welcome your articles, book reviews, clinical cases and any material related to OPA history.▲

**Halyna Troian, CAE**
*Editor*

## CONGRATULATIONS

*To **Dr. Susan Abbey** – recipient of the*

**2009 RCPSC RAC 3 Prix d'excellence Award**

*Dr. Susan Abbey served as OPA President in 2006.*

**CPA PRESIDENT'S COMMENDATION**

***Dr. Doug Weir** (OPA Member),*
***Dr. Bob Buckingham** (OPA President, 2003),*
***Dr. Richard O'Reilly** (OPA President, 2007) and*
***Dr. Sonu Gaind** (OPA President, 2008)*
*were recognized as founding members of the Coalition of Ontario Psychiatrists for their dedication and leadership in developing the Coalition. This group has helped psychiatrists communicate on the policy issues effecting psychiatric care in Ontario. The Coalition has had great success in improving the working conditions for psychiatrists and consequently improving access for patients to psychiatric care.*

**FELLOWS OF THE CPA**

*The honour of Fellow of the CPA was bestowed upon nine CPA member psychiatrists in recognition of their exemplary contributions towards excellence in psychiatry.*

*The CPA's 2009 Fellows are:*
***Dr. Joseph Joel Jeffries** (OPA Member);*
***Dr. Donald A. Wasylenski; Dr. Gary Hnatko;***
***Dr. Raymond Lam; Dr. Phillippa Moss;***
***Dr. Margaret Steele** (OPA President, 2002);*
***Dr. Dhanapal Natarajan;***
***Dr. Deborah Elliott** (OPA Treasurer) and*
***Dr. David Goldbloom** (OPA Member).*

*Please mark your calendars for the*

# OPA 2010 ANNUAL CONFERENCE

April 23 & 24, 2010
Toronto, Ontario
Le Méridien King Edward Hotel

*Stay tuned for our further announcements of the conference program and registration form!*

## ONTARIO PSYCHIATRIC ASSOCIATION (OPA) 2010 ANNUAL CONFERENCE CALL FOR ABSTRACTS

*The OPA Conference Organizing Committee is accepting submissions in the following categories:*

**SYMPOSIUM (2.0 – 2.5 hours)**
Ideally, a symposium should include several participants from different institutions, areas of the province or disciplines.

**WORKSHOP (1.5 – 2.0 hours)**
Workshops focus on specific topics and are particularly aimed at skill transmission including case analysis, skills building or role-play.

**PANEL DISCUSSION (1.5 – 2.0 hours)**
Two or more speakers state their respective viewpoints on a subject. The discussion is moderated, and questions from the floor may be asked.

**VIDEO SESSION (45 – 60 minutes)**
Videos related to psychiatric disorders and mental health issues. The presenter will be asked to introduce and lead a discussion regarding their video.

**POSTER SESSION**
There will be a formal poster session (time to be determined), but we ask that posters be on display throughout the meeting.

**N.B. Under Maintenance of Certification (MOC) Guidelines, all submissions must allocate a minimum of 25% of the time for audience interaction (i.e. discussion period, Q & A).**

**DEADLINE FOR SUBMISSIONS: TUESDAY, DECEMBER 15, 2009.**

*The official submission form may be downloaded from the OPA web site:* ***www.eopa.ca***

# 90 YEARS OF HISTORY – From the OPA Archives

*Those who cannot remember the past are condemned to repeat it.*
— GEORGE SANTAYANA (1863-1952)
from *The Life of Reason, Vol. 1*

In April 2010, the Ontario Psychiatric Association will be officially 90 years old. We plan to celebrate this event at the next Annual meeting which has been moved to April at least partly to commemorate this event. The meeting will be held at Le Méridien King Edward Hotel on the 23rd and 24th of April which is only a few days after the anniversary of the first meeting on the 20th of April, 1920. We will be presenting on the history of the OPA and the history of psychiatry in Ontario and in Canada as well as discussing some of the similarities and differences in clinical practice over that 90 years.

In the next few issues of *Dialogue* we will be giving an overview of the history of the Ontario Psychiatric Association and its forerunner the Ontario Neuro-Psychiatric Association and the social and political environment in which they developed. This will be done by decades.

## 1920-1930

### Post First World War. Expansion of Services.

In 1920, the Great War (World War I) was over for just over a year. Dr. Edward Ryan, the medical superintendent of the O.H. Kingston, (formerly the Rockwood Asylum) invited a large group of people from the other mental hospitals to a meeting where they decided to form the Ontario Neuro-Psychiatric Association. Dr. Ryan became its first President.

In those days the asylums or public mental hospitals made up almost the entire system for mental health care, although there were a few private clinics or small hospitals, and one larger private hospital, *The Homewood Sanitarium* in Guelph. (It was founded as the *Homewood Retreat* in 1883.) There were 9 public mental hospitals, formerly known as "asylums" but now renamed "*Ontario Hospitals for the Insane*". They were located in Toronto (originally the Toronto Asylum, opened in 1850), Langstaff (originally a satellite of the Toronto Asylum, it had been opened in the 1860s but was not open consistently since), Kingston ("Rockwood Asylum", Portsmouth, 1870), London (1870), Hamilton, (first called the "Hospital for Inebriates", but within a year or so renamed the "Hamilton Asylum", 1876), Orillia ("Hospital for the Feeble Minded", 1878), Brockville (1896), Mimico, (later OH New Toronto and Lakeshore Psychiatric Hospital. It was originally built to serve northern Ontario, 1899) and Whitby (1920). General hospital psychiatric units, as we know them today, did not exist.

The Ontario Hospital Whitby had just opened to replace OH Toronto (Queen Street). Dr. J. M. Forster, the medical superintendent of the Ontario Hospital for the Insane Toronto, moved a few hundred patients to the new buildings in a former farmer's field near Port Whitby in the fall of 1919 and officially opened the new hospital on January 1st, 1920 and became its first medical superintendent. He also attended the first meeting in Kingston at which the ONPA was formed and was the second President in 1921. Interestingly, because of overcrowding and pressure on the system, the OH Toronto was not closed as planned. It continues on as the Queen Street mental health Centre and now the Queen Street campus of the Centre for Addictions and Mental Health.

It was a time of expansion and optimism in the mental hospital service. Things were expanding and the future looked promising. At a time before universal health care, only a few of the best known senior neurologist/psychiatrists, usually in large cities, could survive in private practice. Most of the others were employed in the provincial mental hospitals or in other areas of public or hospital service.

Further articles will discuss the next 8 decades of the OPA's history. A capsule summary follows:

## 1930-1940

### The Great Depression and Shadow of War.

The Great Depression started with the stock market crash in October 1929 but did not really bite most people until 1930 and 1931. During this time, governments were cutting back everything, while demands for service were rising. The mental hospitals not only had funding and staffing cuts, they were under great pressure for admissions from many people who had no other place to go. This has sometimes been described as the beginning of the 3 decades of neglect of the mentally ill.

## 1940-1950

### The Second World War and the Postwar Recovery.

During the war, further staff were lost and pressure on mental health services continued to rise. By the end of the conflict, conditions were even worse. Even though there was economic expansion after the war, this period could be described as the second decade of neglect.

## 1950-1960

### The Korean War and the Brain-Washing Experiments.

This was the third decade of neglect. In 1956, the ONPA changed its name to the OPA. By 1959, the overcrowding in the mental hospitals had reached its peak. In the aftermath of the Korean War, there was a great hue and cry about "Brain-washing". In that year there were over 400 patients in Ontario mental hospitals for every 100,000 population. The cry for drastic reform was building in every country.

***EDWARD RYAN, MD –***
***First President of the Ontario Neuro-Psychiatric Association.***
***(From a portrait at the Kingston Psychiatric Hospital.)***

### 1960-1970

**The Reform of Health Care. Expansion of Services.**

This decade was marked by drastic reforms on every level. In 1961 in the U.S.A. a Congressional Committee had published "Action for Mental Health" calling for drastic reforms. In 1963, the Canadian Mental Health Association with considerable federal support published "More for the Mind" which also called for reforms. In 1964, the Royal Commission on Health Services reported to Parliament recommending universal medicare, including full coverage for psychiatric services. Parliament adopted it with all party support and Medicare was born pumping federal money into the system. Mental Health Legislation reform began in Ontario in 1967. Suddenly it was in the interests of the provinces to develop new services. But mental hospitals were not covered by federal cost-sharing so all the new resources went elsewhere. The decline of the mental hospitals had begun.

### 1970-1980

**The Growth of the Mental Health Reform Movement.**

The big thrust was community care. Many were advocating that costs could be cut by closing all the mental hospitals and treating everyone as an out-patient. Groups like the Scientologists and the Mental Health Consumer movement were advocating the shut-down of all psychiatric services or a take-over by consumers (consumer-survivors?).

### 1980-1990

**Cost Containment and Reform Gone Mad.**

By 1980, the rapid expansions of all health services had threatened to outstrip even the generous funding provided by the feds. People became aware of the rising costs; health care costs had risen in Canada from about 7% of Gross Domestic Product to well over 9%. Governments became obsessed with cost-containment. In the U.S., the adoption of 'Managed Care' put mental health services at a particular disadvantage. In Canada, drastic cut-backs in many areas not only threatened services but had the paradoxical effect of increasing costs in the long-run. For the Mental Health Service in Ontario, it was a fight for survival.

### 1990-2000

**The Decade of the Brain.**

Research had been developing rapidly ever since the 1930s and despite some very bad treatments (e.g. psycho-surgery) the whole practice of psychiatry and mental health care had progressed dramatically. The World Health Organization announced this decade as "The Decade of the Brain."

### 2000-2010

**The Chickens Come Home to Roost. Expansion Again.**

With much improvement in knowledge of mental illness and better treatments, it became apparent that the cost-cutting reforms had worsened the system. Governments began to realize that things had been pushed too far and a gradual improvement in conditions occurred. But with past experience as our guide, we must be very aware from where we have come and ever vigilant to prevent the mistakes of the past.▲

**John C. Deadman, MD, DPsych, FRCP(C)**
*Archivist*

# PHYSICIAN'S HEALTH: it's important and it matters

My father, a retired surgeon, often remarks about how good it is that we are helping sick colleagues get help rather than just making sure they don't make major clinical mistakes. I have been working at the OMA's Physician Health Program (PHP) as Associate Medical Director for the past few years and have had the privilege of talking to many physicians who struggle with mental health issues. This past February, I was invited to speak at the Ontario Psychiatric Association's Annual Conference about our programs and in particular our approach to the 'disruptive' physician.

Physicians are actually very healthy compared to the general population and some other professional groups. However, physicians tend to suffer from mental health problems, including substance use disorders, at roughly the same level as the general population. Our training, our position in the health care team and perhaps the dispositional traits that make us successful as physicians may in fact mask our human vulnerability and hinder our decision to seek help or medical attention.

Physician health programs often focus on illness prevention, stress reduction, burnout and ways of improving resilience. There is a continuing need for education and awareness about addressing the ill medical trainee or physician. In addition to providing seminars on these topics, the PHP also connects physicians and trainees to appropriate community resources and we work together with colleagues and/or medical leaders to help suffering doctors who cannot reach out for themselves. Some physicians or trainees require ongoing monitoring and accountability and we often monitor physicians who require a comprehensive program to satisfy regulatory or training requirements.

Emerging evidence points to excellent long-term outcomes for doctors who get treatment and 5-year monitoring for substance dependence. In a recent publication we detailed the outcomes of 100 physicians with substance dependence, 71% never had a relapse and 85% successfully completed the program in good recovery (Brewster et al. BMJ 2008;337:a2098). Less is known about long-term outcomes of physicians with psychiatric disorders such as recurrent major depression and bipolar disorder, and in a upcoming CJP publication (Albuquerque et al. 2009 (Nov) CJP in press) we describe program outcomes for physicians monitored for recurrent major depression and bipolar disorder. In this population, recurrence is the rule and those with comorbid psychiatric conditions appear to be an increased risk for recurrence.

A relatively newer topic is the poorly named 'disruptive physician'. These physicians who come to regulatory attention due to behavioural concerns generally do not have an undetected DSM – IV Axis I disorder. Psychiatrists are attuned to fact that behavioural problems within a workplace are frequently the result of system-wide issues and are not simply attributable to one individual. In the session, we had a lively discussion around the pressures medicine as a whole faces as well as the multiple drivers affecting this focus on behaviour in the workplace. The CPSO task force has published a document to help guide institutions and leaders about a reasonable approach to problematic behaviour that endeavours to respect physicians and protect the public, including colleagues and employees (http:// www.cpso.on.ca/policies/ guidelines/default.aspx?id=2180). The OMA physician health program has been involved in a number of these cases and we are now developing a program (the Physician Workplace Support Program) dedicated to providing broad resources including rehabilitative programs to support the physician and the workplace as they navigate these complex issues.

**PHYSICIANS TEND TO SUFFER FROM MENTAL HEALTH PROBLEMS, INCLUDING SUBSTANCE USE DISORDERS, AT ROUGHLY THE SAME LEVEL AS THE GENERAL POPULATION.**

**THERE IS A CONTINUING NEED FOR EDUCATION AND AWARENESS ABOUT ADDRESSING THE ILL MEDICAL TRAINEE OR PHYSICIAN.**

**PSYCHIATRISTS ARE BEING CALLED UPON TO PLAY A KEY ROLE WITH ASSESSMENT AND/OR TREATMENT OF OUR COLLEAGUES.**

In most aspects of physician health psychiatrists are being called upon to play a key role with assessment and/or treatment of our colleagues. Because physicians characteristically present 'late' in their illness course, access to timely resources is important and sometimes life-saving. Due to the safety sensitive nature of a physician's work, there are a number of relevant issues that treating clinicians need to consider during the course of treatment. There is a need to clarify issues around symptoms and impairment, as well as to clarify the best way to plan a return to work.

You can contact the PHP confidentially if you have questions or concerns at 1-800-851-6606 or visit our website: *www.phpoma.org.*

**Joy Albuquerque, MA, MD, FRCP(C)**
*Associate Medical Director*
*Physician Health Program*
*Ontario Medical Association*

# Update on Relativity

The OMA continues to revise its proposed new methodology (the Comparison of Average Net Daily Income, or CANDI model) for determining 2010 and 2011 relativity allocations. The Section on Psychiatry presented to the relativity Working Group in early October and articulated our ongoing concerns about the original CANDI model, most importantly the lack of any modifier accounting for increased complexity or skills associated with increased years of specialist versus family practice training. At that meeting, the Working Group Chair continued to maintain the CANDI model could not and would not incorporate any such 'complexity' factor.

However, the subsequent revised report the Working Group released *did* include a new "Skills Acquisition Modifier", or SAM, which placed a value on additional years of minimum required post-graduate training [a factor of 4% per year of training, which is consistent with the value placed by the British Columbia relativity model, information the Section cited in supporting our arguments]. The revised model now has both a 'training modifier' and a 'SAM' modifier for additional years of training. It describes the training modifier of lost opportunity cost as "… a null or leveling modifier that equalizes… expected discounted lifetime income…", and specifically differentiates that from the new SAM that "represents a true differential between specialties with different years of training due to additional skills gained…". This is precisely what the Section had been arguing for.

This represents a 180 degree shift in the Working Group's position on this issue. Successfully pressuring the Working Group to change its stance, despite months of resistance, shows the strength of arguments and effectiveness of the campaign we were able to mobilize to ensure the OMA acknowledged value of additional specialty training.

While no methodology is without its imperfections, acknowledging added complexity/skills with the new SAM factor is a significant positive improvement in CANDI that addresses the Section's strongest criticism of the original CANDI model. The Working Group will present its report to OMA General Council in late November, the decision regarding continuing with the existing RVIC model or adopting the new CANDI model for 2010 relativity allocations will be made by OMA General Council at that meeting.

Lastly, by the time you read this you should already have benefited from the relativity increase associated with 2009 allocations, which were scheduled to be implemented October 1. As per previous correspondence, the 3% 'top up' was to stop October 1, and be replaced by psychiatry's total allocation increase of 9.5% (distributed amongst various codes, as previously communicated) [by comparison, groups not receiving any relativity allocation in 2009 only received a 2.5% increase].▲

**K. Sonu Gaind, MD, FRCP(C)**
*Past President, Ontario Psychiatric Association*
*Tariff Chair, OMA Section on Psychiatry*

# President's Message

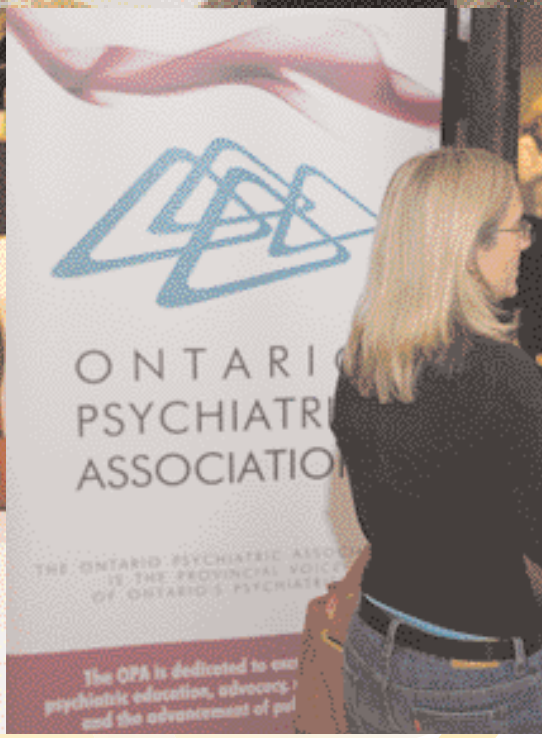
*continued from page 1*

The definition of recovery in this report must be expanded. It currently reads, "The recovery approach looks at the whole person and defines the person positively, focusing on their strengths and goals rather than their illness". Is it not possible to do both? I think recovery is definitely more than just the absence of disease and I hope this was the authors' intended message. Can we not address treatment and highlight individual strengths and goal-based initiatives concurrently? The role of the countless numbers of psychiatrists conveying quality mental health care in private practice appear to have been overlooked. What will be their role in this "transformed system". These and many other key concerns can only briefly be captured in this response.

We are committed to labouring with inter-governmental agencies on this ambitious plan. It is our desire to partner with key stakeholders to promote change that is thoughtful, progressive and sustainable. We are motivated professional partners who wish to collaborate with other care providers, families and individual patients to create accepting and caring communities. We will actively seek a voice on behalf of members to make appropriate changes that optimize the health and well being of those in need. We will also stress the need for accountability of our elected officials and their appointed bureaucratic representatives to fund a system in such a manner that the goals articulated can be obtained. We build on a rich history and many past successes and look forward to facilitating meaningful dialogue. We wholeheartedly agree with the minister that there is no health care without mental health care. We hope this ministry's expressed goals will be adequately resourced to achieve these objectives. With the appointment of Deb Matthews as the new Ontario Minister of Health and Long Term Care we hope this momentum will not be lost.▲

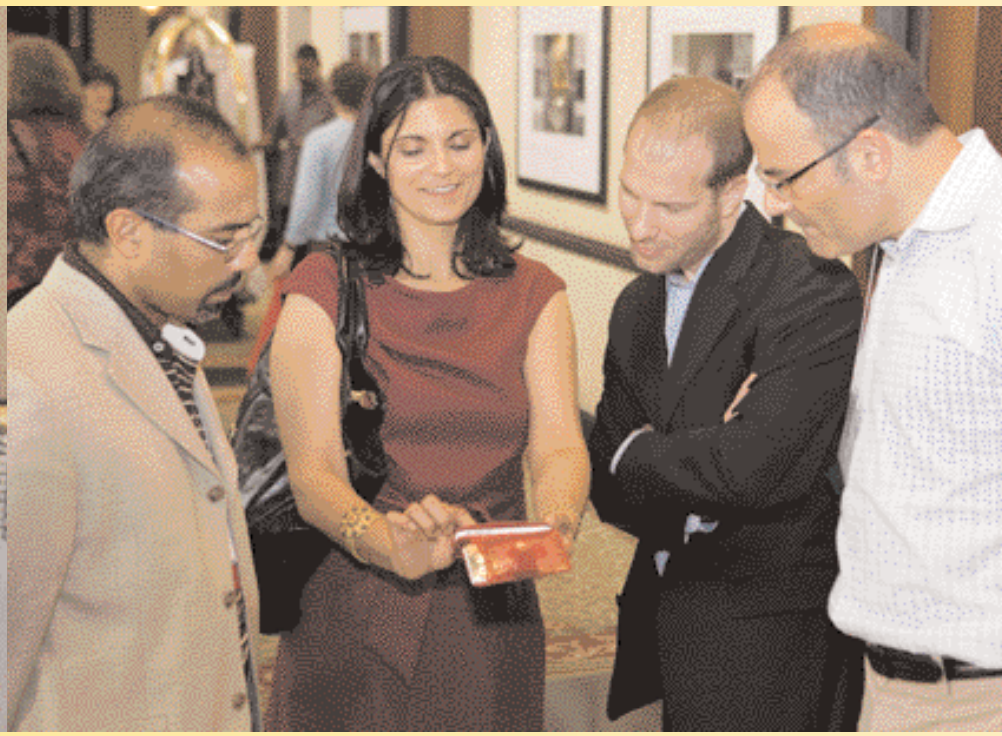
**P. Mulzer, MD, FRCP(C)**
*President, Ontario Psychiatric Association*

# OPA 2009 Psychotherapy Section's Fall Conference.



## . . September 26, 2009

*OPA Conference Planning Committee and Executive (l-r) — Jon Novick, Madhu Vallabhaneni, Doron Almagor (OPA President-Elect), Nancy McWilliams (Guest Speaker), Tina Chadda (Committee Chair), Paul Mulzer (OPA President), Sonu Gaind (OPA Past President).*



# Clinical Vignette

Matt S. is a 17 year old high school senior who is abandoned by his friends in the ER waiting room of your local, rural hospital. He is immediately attended by triage staff who note the following presentation: pulse 150 bpm and regular, blood pressure 119/96, temp 40.3 C. He is obtunded, clammy, diaphoretic and appears moderately dehydrated. He is wearing a fluorescent bracelet and a soother!

As per protocol you begin the ABC of resuscitation, he is rapidly cooled and rehydrated. His oxygen saturations are excellent. Of course, as part of your evaluation you perform a neurological assessment and note pinpoint pupils. You give him a trial of naloxone and he rouses and you start a protocol to address his opiate overdose as well as his hyperthermic state induced by ecstasy. If you had overlooked his severe opiate intoxication which includes Oxycontin, Percocet and Morphine, in addition to street methadone, he may not have survived the night. In this community hospital his urine drug screen, when available, confirms your diagnostic impression but arrives at a time when it cannot influence your decision making. This is like the presentations commonly encountered in the emergency.

Take Home Messages:

1. Modern raves often include participants raiding the medicine cabinet dumping pills into a bowl and taking out a handful. Patients frequently have no idea what they have taken. Rapid urine dip screening strips can help if available while quantitative testing is pending. In the severely dehydrated you may find it difficult to get even catheter urine. Often your clinical judgement will require your careful review of the case. You need to have a basic understanding of common presentation of intoxicated and withdrawal states and what is lethal. In a patient with reduced level of arousal, after assessing for head trauma, metabolic, etc. include opiate intoxication in your differential. A test naloxone dose can be a valuable tool to differentiate. Remember it will put someone in an immediate state of withdrawal.

2. The modern face of psychiatry will involve an enhanced understanding of concurrent disorders. In fact, over time this term will be replaced by comprehensive psychiatric care which will be understood to include both disciplines.

3. A percentage of your refractory patients have an undiagnosed substance use disorder and the higher their status the less likely it will be diagnosed. A sleep disorder may accompany this and may be secondary to substance concerns.▲

**P. Mulzer, MD, FRCP(C)**
*President, Ontario Psychiatric Association*

# The Importance of Psychotherapy in Psychiatric Training

After attending the Fall OPA Psychotherapy Conference, one may reflect upon the importance of Psychotherapy training in a Psychiatry Residency. For many years, Nancy McWilliams' writing has been used to teach Psychodynamic Concepts to Psychiatry Residents. Her lectures, infused with personal clinical examples, demonstrate how a psychodynamic understanding of a patient can simply and effectively be incorporated into clinical practice. Throughout her talk, McWilliams provided examples of the application of these psychodynamic concepts in settings outside of the Psychotherapy office. This is of particular importance for Residents in the early stages of their careers.

In the course of a Psychiatry Residency, one is often forced to learn in the pressured clinical environments of busy outpatient clinics, Emergency Departments and Inpatient Units. Residents are constantly balancing the needs of patients with his or her own learning needs. Under the weight of this pressure, the psychodynamic complexity of our clinical interactions may be overlooked. Transferential and Countertransferential dynamics seem particularly potent to the novice trainee and, while the psychodynamics of an interaction may not have been overtly addressed, the emotional residue may linger with us long after the clinical encounter is over. Residents who have a poor understanding of Psychodynamic Psychiatry may run the risk of feeling overwhelmed by these interactions and possibly suffering from emotional burnout early in their careers.

Recent trends in training programs have seen Residents dividing themselves into "those who will" and "those who will not" do psychotherapy as part of their future careers. This may reflect a naivety on behalf of early-stage trainees who do not recognize that even the most "biological" psychiatrists intuitively use psychodynamic concepts guide interactions with their patients. This dichotomy becomes incorporated into our understanding of psychiatry early in our training, thereby potentially undermining the protection that comes with achieving the balance of both approaches in practice. While teaching Psychodynamic concepts in the context of Psychotherapy Supervision is important, Residents may not intuitively know the importance of applying these concepts to work outside of Psychotherapy. It is therefore important to continue to find ways to teach Psychodynamic concepts in a variety of settings so that all Residents have the opportunity to see how Psychodynamic concepts can enrich their clinical work.▲

**Nadia Aleem, PGY 5, University of Western Ontario**

Seroquel XR

# Prescribing Summary

## Patient Selection Criteria

Therapeutic classification: Antipsychotic/Antidepressant agent

### INDICATIONS AND CLINICAL USE

***Adults:*** SEROQUEL XR® (quetiapine fumarate extended-release) is indicated for the symptomatic relief of major depressive disorder (MDD) when currently available approved antidepressant drugs have failed either due to lack of efficacy and/or lack of tolerability. While there is no evidence that the efficacy of SEROQUEL XR is superior to other antidepressants, it provides a treatment option for patients who have failed on previous antidepressant treatments. Clinicians must take into account the safety concerns associated with antipsychotic drugs, a class of drugs to which SEROQUEL XR belongs. Safety concerns of this class include: weight gain, hyperlipidemia, hyperglycaemia, tardive dyskinesia and neuroleptic malignant syndrome (see WARNINGS AND PRECAUTIONS). SEROQUEL XR should only be prescribed in patients with MDD by clinicians who are aware of the importance and are experienced in the early detection and management of the above-mentioned safety issues associated with this class. Long-term safety of SEROQUEL XR in MDD has not been systematically evaluated. Thus, the physician who elects to use SEROQUEL XR in the treatment of MDD should use SEROQUEL XR for the shortest time that is clinically indicated. When lengthier treatment is indicated, the physician must periodically reevaluate the long-term usefulness of the drug for the individual patient keeping in mind the long-term risks (see SUPPLEMENTAL PRODUCT INFORMATION). ***Geriatrics (>65 years of age):*** SEROQUEL XR is not indicated in elderly patients with dementia (See Serious Warnings and Precautions box and Special Populations). ***Pediatrics (<18 years of age):*** The safety and efficacy of SEROQUEL XR in children under the age of 18 years have not been established.

SEROQUEL XR is also indicated for the management of the manifestations of schizophrenia, as monotherapy for the acute management of manic episodes associated with bipolar disorder and as monotherapy for the acute management of depressive episodes associated with bipolar I and bipolar II disorder. Please consult the Product Monograph for complete prescribing information.

### CONTRAINDICATIONS

SEROQUEL XR (quetiapine fumarate extended-release) is contraindicated in patients with a known hypersensitivity to this medication or any of its ingredients.

### Special Populations

***Pregnant Women:*** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with SEROQUEL XR. The safety and efficacy of SEROQUEL XR during human pregnancy have not been established. Therefore, SEROQUEL XR should only be used during pregnancy if the expected benefits justify the potential risks. ***Nursing Women:*** The degree to which quetiapine is excreted into human milk is unknown. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking SEROQUEL XR. ***Pediatrics (<18 years of age):*** The safety and efficacy of SEROQUEL XR in children under the age of 18 years have not been established. ***Geriatrics (≥65 years of age):*** The number of patients 65 years of age or over exposed to SEROQUEL XR during clinical trials was limited (n=68). When compared to younger patients the mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly subjects. In addition, as this population has more frequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication, caution should be exercised with the use of SEROQUEL XR in the elderly patient (see ADMINISTRATION). In a clinical trial that evaluated non-demented elderly patients (aged 66 to 89 years) with MDD, the tolerability of SEROQUEL XR once daily was comparable to that seen in adults (aged 18-65 years) other than the incidence of extrapyramidal symptoms (see WARNINGS AND PRECAUTIONS, Neurologic, Tardive Dyskinesia [TD] and Extrapyramidal Symptoms [EPS]). **Use in Geriatric Patients with Dementia: Overall Mortality: Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs. In two placebo-controlled trials with oral SEROQUEL in this population, the incidence of mortality was 5.5% for SEROQUEL-treated patients compared to 3.2% for placebo-treated patients. SEROQUEL XR is not indicated in elderly patients with dementia.** ***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 XR and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

# Safety Information

### WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

**Increased Mortality in Elderly Patients with Dementia**

**Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in death rate in the drug-related patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.**

**General:** ***Body Temperature Regulation:*** Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL XR (quetiapine fumarate extended-release) for patients who will be experiencing conditions which may contribute to an elevation of core temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity or being subject to dehydration. ***Acute Withdrawal (Discontinuation) Symptoms:*** Acute discontinuation symptoms such as insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability have been described after abrupt cessation of antipsychotic drugs including SEROQUEL XR. Gradual withdrawal over a period of at least one to two weeks is advisable. Symptoms usually resolved after 1 week post-discontinuation. **Cardiovascular:** ***Hypotension and Syncope:*** As with other drugs that have high α$_1$-adrenergic receptor blocking activity, SEROQUEL XR may induce orthostatic hypotension, dizziness and sometimes syncope, especially during the initial dose-titration period. These events may lead to falls. In placebo-controlled SEROQUEL XR trials, there was little difference in the adverse reaction reporting rate of syncope in patients treated with SEROQUEL XR (0.5%, 11/2388) compared to patients on placebo (0.3%, 4/1267). Syncope was reported in 1% (35/4083) of patients treated with SEROQUEL (quetiapine, immediate-release formulation), compared with 0.3% (3/1006) on placebo and 0.4% (2/527) on active control drugs. SEROQUEL XR should be used with caution in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or other conditions predisposing to hypotension (e.g., dehydration, hypovolemia and treatment with antihypertensive medications) (see OVERDOSAGE). ***Cholesterol and Triglyceride Elevations:*** Very common (>10%) cases of elevations in serum triglyceride levels (>2.258 mmol/L on at least one occasion) and elevations in total cholesterol (predominantly LDL cholesterol) (≥6.2064 mmol/L on at least one occasion) have been observed during treatment with quetiapine in clinical trials (see ADVERSE REACTIONS). Lipid increases should be managed as clinically appropriate. In 6-week MDD monotherapy clinical trials, SEROQUEL XR-treated patients had increases from baseline in mean triglycerides of 8%, compared to a mean decrease of 1% for placebo-treated patients. In the same trials, both SEROQUEL XR- and placebo-treated patients had decreases from baseline in mean cholesterol of 1% and 3%, respectively. In a longer-term randomized withdrawal MDD trial, patients who completed at least 158 days of SEROQUEL XR treatment (n=196) showed mean increases from baseline in triglycerides of approximately 5% and mean decreases from baseline in cholesterol of approximately 4%. **Endocrine and Metabolism:** ***Hyperglycaemia:*** As with some other antipsychotics, hyperglycaemia and diabetes mellitus (including exacerbation of pre-existing diabetes, diabetic ketoacidosis and diabetic coma including some fatal cases) in the aggregate have been reported rarely (≥0.01% - <0.1%) during the use of quetiapine in post-marketing experience, sometimes in patients with no reported history of hyperglycaemia (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). Blood glucose increases to hyperglycaemic levels (fasting blood glucose ≥7.0 mmol/L or a nonfasting blood glucose ≥11.1 mmol/L on at least one occasion) have been observed commonly (≥1% - <10%) with quetiapine in clinical trials. Occasional reports of diabetes have also been observed in clinical trials with quetiapine (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings). Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemic during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. ***Hyperprolactinaemia:*** During clinical

trials with quetiapine, elevation in prolactin levels occurred in 3.6% (158/4416) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo (see ADVERSE REACTIONS). Increased prolactin levels with quetiapine were observed in rat studies. As is common with compounds which stimulate prolactin release, the administration of quetiapine resulted in an increase in the incidence of mammary neoplasms in rats. The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear. To date, neither clinical nor epidemiological studies have shown an association between chronic administration of drugs that stimulate prolactin release, and mammary tumourigenesis. Tissue culture experiments, however, indicate that approximately one third of human breast cancers are prolactin dependent in vitro; a factor of potential importance if prescription of these drugs is contemplated in a patient with previously detected breast cancer. Possible manifestations associated with elevated prolactin levels are amenorrhea, galactorrhea and mastodynia. **Hypothyroidism:** In SEROQUEL XR clinical trials, 0.2% (4/1755) of patients on SEROQUEL XR compared to 0% (0/796) on placebo experienced decreased free thyroxine and 2.7% (46/1716) on SEROQUEL XR compared to 1.4% (11/785) on placebo experienced increased TSH; however, no patients experienced a combination of clinically significant decreased free thyroxine and increased TSH. In clinical trials, on average SEROQUEL was associated with about a 20% mean reduction in thyroxine levels (both total and free). Forty-two percent of SEROQUEL-treated patients showed at least a 30% reduction in total $T_4$ and 7% showed at least a 50% reduction. Maximum reduction of thyroxine levels generally occurred during the first two to four weeks of treatment with SEROQUEL. These reductions were maintained without adaptation or progression during longer-term treatment. Decreases in $T_4$ were not associated with systematic changes in TSH or clinical signs or symptoms of hypothyroidism. Approximately 0.4% (12/2595) of patients treated with SEROQUEL experienced persistent increases in TSH, and 0.25% of patients were treated with thyroid replacement. **Weight Gain:** In 6-week placebo-controlled MDD acute monotherapy clinical trials, for patients treated with SEROQUEL XR mean weight gain was 0.87 kg (n=1149) compared to 0.31 kg (n=648) in patients treated with placebo. In a longer-term randomized withdrawal MDD trial, patients who completed at least 158 days of SEROQUEL XR treatment (n=196), mean weight gain for patients in SEROQUEL XR 50, 150 and 300 mg/day groups was 1.0 kg, 2.5 kg and 3.0 kg, respectively. In these same patients the percentage of patients experiencing a weight increase of ≥7% by 158 days in SEROQUEL XR 50, 150 and 300 mg/day groups was 13%, 24% and 33%, respectively. Based on the cumulative acute placebo-controlled clinical trial database, weight gain (based on ≥7% increase in body weight from baseline) was reported in 9.6% in quetiapine-treated patients and 3.8% in placebo-treated patients, which occurs predominantly during the early weeks of treatment in adults. **Gastrointestinal: Antiemetic Effect:** Consistent with its dopamine antagonist effects, SEROQUEL XR may have an antiemetic effect. Such an effect may mask signs of toxicity due to overdosage of other drugs, or may mask symptoms of disease such as brain tumour or intestinal obstruction. **Hematologic: Neutropenia:** Severe neutropenia (<0.5 x $10^9$/L) has been uncommonly reported in quetiapine clinical trials. There was no apparent dose relationship. Possible risk factors for leucopenia and/or neutropenia include pre-existing low white cell count (WBC) and history of drug-induced leucopenia and/or neutropenia. SEROQUEL XR should be discontinued in patients with a neutrophil count <1.0 x $10^9$/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 x $10^9$/L) (see ADVERSE REACTIONS, Abnormal Haematologic and Clinical Chemistry Findings and Post-Market Adverse Drug Reactions). **Hepatic: Hepatic Impairment:** Decreased clearance of SEROQUEL was observed in patients with mild hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). No pharmacokinetic data are available for quetiapine in patients with moderate or severe hepatic impairment. However, should clinical judgement deem treatment with SEROQUEL XR necessary, the drug should be used with great caution in patients with moderate or severe hepatic impairment (see ADMINISTRATION). **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) associated with SEROQUEL XR 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 placebo-controlled trials were approximately 1% for both SEROQUEL XR and placebo. During premarketing clinical trials, therapy with SEROQUEL was associated with elevation of hepatic transaminases, primarily ALT. Precautions should be exercised when using SEROQUEL XR in patients with pre-existing hepatic disorders, in patients who are being treated with potentially hepatotoxic drugs, or if treatment-emergent signs or symptoms of hepatic impairment appear. For patients who have known or suspected abnormal hepatic function prior to starting SEROQUEL XR, standard clinical assessment, including measurement of transaminase levels, is recommended. Periodic clinical reassessment with transaminase levels is recommended for such patients, as well as for patients who develop any signs and symptoms suggestive of a new onset liver disorder during SEROQUEL XR therapy. **Neurologic: Neuroleptic malignant syndrome (NMS):** Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including SEROQUEL XR. The clinical manifestations of NMS are hyperthermia, 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. In arriving at a diagnosis, it is important to identify 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. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system pathology. The management of NMS should include immediate discontinuation of antipsychotic drugs, including SEROQUEL XR, and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring; and treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated 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 (TD) and Extrapyramidal Symptoms (EPS):** Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that 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 estimates to predict which patients are likely to develop the syndrome. In short-term placebo-controlled monotherapy clinical trials in MDD the aggregated incidence of EPS was 5.4% for SEROQUEL XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with MDD, the aggregated incidence of EPS was 9.0% for SEROQUEL XR and 2.3% for placebo. In long-term studies of schizophrenia, bipolar disorder and MDD the aggregated exposure-adjusted incidence of treatment-emergent EPS was similar between quetiapine and placebo. The risk of developing TD 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 TD, 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 XR should be prescribed in a manner that is most likely to minimize the occurrence of TD. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that is known to respond to antipsychotic drugs, and 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 TD appear in a patient on SEROQUEL XR, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL XR despite the presence of the syndrome. **Seizures:** In controlled clinical trials with SEROQUEL XR, there was no difference in the incidence of seizures in patients treated with SEROQUEL XR (0.04%, 1/2588) or placebo (0.2%, 3/1267). Nevertheless, as with other antipsychotics, caution is recommended when treating patients with a history of seizures or with conditions associated with a lowered seizure threshold (see ADVERSE REACTIONS). **Potential Effect on Cognitive and Motor Performance:** Somnolence was a very commonly reported adverse event in patients treated with SEROQUEL XR, especially during the initial dose-titration period. Since SEROQUEL XR may cause sedation and impair motor skill, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, until they are reasonably certain that therapy with SEROQUEL XR does not affect them adversely. Somnolence may lead to falls. **Ophthalmologic: Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies at 4 times the recommended human dose. Lens changes have also been observed in patients during long-term SEROQUEL treatment but a causal relationship to SEROQUEL use has not been established. The possibility of lenticular changes during long-term use of SEROQUEL XR in man thus can not be excluded at this time. Eye examinations (e.g., slit lamp exams) prior to or shortly after initiation of treatment with SEROQUEL XR and at 6-month intervals thereafter, are recommended. If clinically significant lens changes associated with SEROQUEL XR use are observed, discontinuation of SEROQUEL XR should be considered. Psychiatric: Suicide/Suicidal Thoughts or Clinical Worsening:** Depressive episodes are associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission of depression occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events are also known to be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. In MDD acute clinical trials, the incidence of treatment-emergent suicidal ideation or suicide attempt was 0.7% in SEROQUEL XR-treated patients and 0.7% in placebo-treated patients. In a longer-term randomized withdrawal study in patients with MDD, the incidence during randomized treatment was 0.3% for SEROQUEL XR and 0.5% for placebo. **Renal:** There is little experience with SEROQUEL XR in patients with renal impairment, except in a few (subclinical) single-dose study with SEROQUEL. SEROQUEL XR should thus be used with caution in patients with known renal impairment, especially during the initial dosing period (see ADMINISTRATION).

## ADVERSE REACTIONS

**Commonly Observed Adverse Events in Short-Term Placebo-Controlled Clinical Trials:**

The most commonly observed adverse events associated with the use of SEROQUEL XR (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo) during acute monotherapy with SEROQUEL XR were dry mouth, sedation, somnolence, dizziness and fatigue.

**Adverse Events Associated With Discontinuation in Short-Term Placebo-Controlled Clinical Trials:**

In placebo-controlled monotherapy MDD trials, 14.3% of patients on SEROQUEL XR discontinued due to adverse events compared to 4.5% on placebo. In a placebo-controlled monotherapy trial in elderly patients with

MDD, 9.6% of patients on SEROQUEL XR discontinued due to adverse events compared to 4.1% on placebo.

To report adverse events:
AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario
L4Y 1M4
www.astrazeneca.ca
T 1-800-433-0733
F 1-800-267-5743

## DRUG INTERACTIONS

**Drug-Drug Interactions:** Given the primary central nervous system effects of quetiapine, SEROQUEL XR (quetiapine fumarate extended-release) should be used with caution in combination with other centrally acting drugs (see SUPPLEMENTAL PRODUCT INFORMATION).

## Administration

SEROQUEL XR (quetiapine fumarate extended-release) tablets should be swallowed whole and not split, chewed or crushed. SEROQUEL XR can be administered with or without food. SEROQUEL XR should be administered once daily, generally in the evening (see INDICATIONS AND CLINICAL USE). Usual Dose: The titration rate, based on the clinical trials, is shown in the table below.

| | Day 1 | Day 2 | Day 3 |
|---|---|---|---|
| Once-daily dosing | 50 mg | 50 mg | 150 mg |

The usual target dose is 150 mg. Some patients may respond to doses as low as 50 mg/day and, where clinically indicated, dose may be increased to 300 mg/day after Day 4. In clinical trials, doses between 50-300 mg/day were shown to be efficacious; however, the incidence of certain adverse events increased with dose. In MDD, the safety of doses above 300 mg/day has not been evaluated. Some of the safety concerns associated with SEROQUEL XR and this class of agents (i.e., antipsychotics) may be dose-related. The SEROQUEL XR dose should thus be periodically reassessed to achieve and maintain the lowest effective dose. Furthermore, as the long-term safety of SEROQUEL XR in MDD has not been systematically evaluated, the physician who elects to use SEROQUEL XR in the treatment of MDD should use SEROQUEL XR for the shortest time that is clinically indicated. When long-term treatment is believed to be indicated, the physician must periodically re-evaluate the long-term usefulness of the drug for the individual patient keeping in mind the long-term risks. ***Switching Patients From SEROQUEL Tablets to SEROQUEL XR Tablets:*** For more convenient dosing, patients who are currently being treated with divided doses of SEROQUEL (quetiapine, immediate-release formulation) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary. ***Switching Patients From Other Antidepressants:*** For many antidepressants a gradual taper is recommended prior to complete discontinuation of the drug (physicians should refer to the approved Product Monograph of the specific antidepressant). There are no systematically collected data to address switching patients from other antidepressants to SEROQUEL XR. Generally there should be no need for a wash-out period between stopping an antidepressant and starting SEROQUEL XR. The physician may elect to initiate SEROQUEL XR treatment while tapering the antidepressant; however, patients may experience additive side effects during the overlap period. **Dosing Considerations in Special Populations:** ***Elderly:*** As with other antipsychotics, SEROQUEL XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of SEROQUEL XR may need to be slower, and the daily therapeutic target dose lower, than that used in younger patients. In clinical trials, 68 patients, 65 years of age or over, were treated with SEROQUEL XR. Given the limited experience with SEROQUEL XR in the elderly, and the higher incidence of concomitant illness and concomitant medication in this population, SEROQUEL XR should be used with caution. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly subjects when compared to younger patients. Elderly patients should be started on the lowest available dose (i.e., 50 mg/day) of SEROQUEL XR. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance of the individual patient. In elderly patients with MDD, initial dosing should begin at 50 mg on Days 1-3, the dose can be increased to 100 mg on Day 4, and 150 mg on Day 8. ***Hepatic Impairment:*** Quetiapine is extensively metabolized by the liver. Therefore, SEROQUEL XR should be used with caution in patients with mild hepatic impairment, especially during the initial dosing period. Patients with mild hepatic impairment should be started on the lowest available dose (i.e., 50 mg/day) of SEROQUEL XR. The dose should be increased daily in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance in the individual patient. No pharmacokinetic data are available for quetiapine in patients with moderate to severe hepatic impairment. However, should clinical judgement deem treatment with SEROQUEL XR necessary, the drug should be used with great caution in patients with moderate or severe hepatic impairment (see WARNINGS AND PRECAUTIONS, Hepatic). ***Renal Impairment:*** As clinical experience is lacking, caution is advised (see WARNINGS AND PRECAUTIONS, Renal). **Missed Dose:** SEROQUEL XR should be taken at the same time each day. If a previous day's dose has been missed, administration should be resumed the next day at the normal administration time. **Dosage Forms and Packaging:** SEROQUEL XR (quetiapine fumarate extended-release) is available as film-coated tablets containing quetiapine fumarate equivalent to 50, 150, 200, 300 or 400 mg of quetiapine free base as follows: 50 mg quetiapine tablets are peach coloured, capsule-shaped, biconvex, imprinted with "XR 50" on one side and plain on the other, available in high-density polyethylene (HDPE) bottles of 60 tablets. 150 mg quetiapine tablets are white, capsule-shaped, biconvex, imprinted with "XR 150" on one side and plain on the other, available in HDPE bottles of 60 tablets. 200 mg quetiapine tablets are yellow, capsule-shaped, biconvex, imprinted with "XR 200" on one side and plain on the other, available in HDPE bottles of 60 tablets. 300 mg quetiapine tablets are pale yellow, capsule-shaped, biconvex, imprinted with "XR 300" on one side and plain on the other, available in HDPE bottles of 60 tablets. 400 mg quetiapine tablets are white, capsule-shaped, biconvex, imprinted with "XR 400" on one side and plain on the other, available in HDPE bottles of 60 tablets. SEROQUEL XR is available in 5 strengths containing 50, 150, 200, 300 or 400 mg quetiapine per tablet (as quetiapine fumarate). The core of the tablet contains the excipients hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium citrate. The coating of the tablet contains hydroxypropyl methylcellulose, polyethylene glycol 400, red ferric oxide (50 mg tablets), titanium dioxide and yellow ferric oxide (50, 200 and 300 mg tablets).

## SUPPLEMENTAL PRODUCT INFORMATION

**Adverse Reactions**

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. **Clinical Trial Adverse Drug Reactions:** 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 figures cited, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence in the population studied.

**Table 1: Adverse Events Reported for at Least 1% of SEROQUEL XR-Treated Subjects (Doses Ranging From 50 to 300 mg/day) and for a Higher Percentage of SEROQUEL XR-Treated Subjects Than Subjects Who Received Placebo in Short-Term, Placebo-Controlled MDD Monotherapy Phase II Trials**

| Body System and MedDRA Term[a] | Percentage of Subjects With Adverse Events[b] | |
|---|---|---|
| | SEROQUEL XR (n=1149) | Placebo (n=440) |
| **General disorders and administration site conditions** | | |
| Fatigue | 7 | 2 |
| Irritability | 4 | 3 |
| **Nervous system disorders** | | |
| Sedation | 28 | 6 |
| Somnolence | 24 | 7 |
| Dizziness | 14 | 8 |
| Disturbance in attention | 2 | <1 |
| Hypersomnia | 2 | <1 |
| Lethargy | 2 | 1 |
| **Gastrointestinal system disorders** | | |
| Dry mouth | 35 | 8 |
| Constipation | 8 | 4 |
| Vomiting | 3 | 1 |
| Dyspepsia | 4 | 3 |
| **Metabolic and nutritional disorders** | | |
| Increased appetite | 5 | 3 |
| Weight increased | 3 | <1 |
| **Musculoskeletal and connective tissue disorders** | | |
| Back pain | 3 | 2 |
| Myalgia | 3 | 2 |
| Musculoskeletal stiffness | 2 | 1 |
| **Psychiatric disorders** | | |
| Abnormal dreams | 2 | 1 |
| **Respiratory disorders** | | |
| Nasal congestion | 2 | 1 |
| **Special senses** | | |
| Vision blurred | 3 | 2 |

[a] Events for which SEROQUEL XR incidence was equal to or less than placebo are not listed in the table. Table reports percentage rounded to the nearest integer.

[b] Patients with multiple events falling under the same preferred term are counted only once in that term.

[c] The following adverse events occurred in 1% of patients treated with SEROQUEL XR compared to <1% in placebo: chills, dysarthria, dyspepsia, sluggishness, diarrhea, dizziness postural, tachycardia, restless legs syndrome, gastroesophageal reflux disease, pharyngolaryngeal pain and melaena.

**Table 2: Dose-Related Adverse Events in ≥1% of Patients Treated With SEROQUEL XR (Doses 50, 150 and 300 mg/day) Where the Incidence of the Adverse Events in Patients Treated With SEROQUEL XR 150 mg and/or 300 mg was Greater Than the Incidence in SEROQUEL XR 50 mg and Placebo-Treated Patients in Short-Term Fixed-Dose, Placebo-Controlled MDD Monotherapy Phase III Trials**

| Body System and MedDRA Term[a] | Percentage of Subjects With Adverse Events[b] | | | |
|---|---|---|---|---|
| | Placebo (n=330) | SEROQUEL XR 50 mg (n=151) | SEROQUEL XR 150 mg (n=328) | SEROQUEL XR 300 mg (n=311) |
| **General disorders and administration site conditions** | | | | |
| Pain | 0 | 1 | 1 | 2 |
| Chills | 0 | 1 | 0 | 2 |
| **Nervous system disorders** | | | | |
| Sedation | 6 | 27 | 37 | 34 |
| Somnolence | 9 | 18 | 22 | 28 |
| Dizziness | 8 | 9 | 10 | 15 |
| Dysarthria | 0 | 1 | 1 | 2 |

| Body System and MedDRA Term[a] | Percentage of Subjects With Adverse Events* | | | |
|---|---|---|---|---|
| | Placebo (n=3339) | SEROQUEL XR 50 mg (n=181) | SEROQUEL XR 150 mg (n=1204) | SEROQUEL XR 300 mg (n=1311) |
| Dizziness in attention | 0 | 1 | 2 | 2 |
| Hypoesthesia | 1 | 0 | 1 | 2 |
| Akathisia | 1 | 0 | 2 | 1 |
| Lethargy | 1 | 2 | 3 | 1 |
| Paraesthesia | 1 | 1 | 2 | 1 |
| Hypersomnia | 0 | 1 | 2 | 1 |
| **Gastrointestinal system disorders** | | | | |
| Dry mouth | 9 | 22 | 36 | 43 |
| Constipation | 4 | 7 | 7 | 9 |
| Nausea | 8 | 8 | 12 | 9 |
| Vomiting | 2 | 2 | 4 | 5 |
| Dyspepsia | 3 | 2 | 5 | 4 |
| Gastroesophageal reflux disease | 0 | 0 | 1 | 2 |
| Abdominal distension | 1 | 0 | 0 | 2 |
| Abdominal pain | 1 | 1 | 2 | 1 |
| **Cardiovascular disorders** | | | | |
| Tachycardia | 0 | 1 | 2 | 1 |
| **Metabolic and nutritional disorders** | | | | |
| Increased appetite | 3 | 4 | 5 | 4 |
| Weight increased | 1 | 1 | 2 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Back pain | 2 | 2 | 5 | 5 |
| Arthralgia | 2 | 2 | 3 | 0 |
| Myalgia | 2 | 4 | 5 | 0 |
| Muscle tightness | 1 | 1 | 0 | 2 |
| **Psychiatric disorders** | | | | |
| Anxiety | 2 | 1 | 2 | 0 |
| Abnormal dreams | 3 | 2 | 4 | 2 |
| Restlessness | 0 | 0 | 1 | 2 |
| Nightmare | 1 | 1 | 1 | 2 |
| **Infections and infestations** | | | | |
| Nasopharyngitis | 3 | 2 | 4 | 3 |
| Gastroenteritis | 0 | 1 | 2 | 1 |
| **Respiratory disorders** | | | | |
| Nasal congestion | 2 | 1 | 2 | 3 |
| Sinus congestion | 1 | 1 | 2 | 2 |
| Dyspnoea | 1 | 1 | 1 | 2 |
| Epistaxis | 0 | 1 | 0 | 2 |
| Nasal dryness | 0 | 0 | 1 | 1 |
| **Special senses** | | | | |
| Vision blurred | 1 | 2 | 3 | 5 |

* Events for which SEROQUEL XR incidence was equal to or less than placebo are not listed in the table.

a Patients with multiple events falling under the same preferred term are counted only once in that term.

**Table 3: Adverse Events Reported for at Least 1% of SEROQUEL XR-Treated Subjects (Doses Ranging From 50 to 300 mg/day) and for a Higher Percentage of SEROQUEL XR-Treated Subjects Than Subjects Who Received Placebo in a Short-Term, Placebo-Controlled Elderly MDD Monotherapy Phase III Trial**

| Body System and MedDRA Term[a] | Percentage of Subjects With Adverse Events* | |
|---|---|---|
| | SEROQUEL XR (n=166) | Placebo (n=172) |
| **General disorders and administration site conditions** | | |
| Fatigue | 8 | 5 |
| Asthenia | 4 | 1 |
| **Nervous system disorders** | | |
| Somnolence | 33 | 8 |
| Headache | 19 | 14 |
| Dizziness | 18 | 15 |
| Sedation | 5 | 1 |
| Dysgeusia | 2 | 1 |
| Balance disorder | 2 | 1 |
| Dizziness postural | 2 | 1 |
| Akathisia | 2 | 1 |
| **Gastrointestinal disorders** | | |
| Dry mouth | 20 | 10 |
| Constipation | 5 | 2 |
| Abdominal pain upper | 3 | 2 |
| Dyspepsia | 2 | 1 |
| **Cardiovascular system disorders** | | |
| Hypotension | 2 | 0 |
| **Metabolic and nutritional disorders** | | |
| Weight increased | 5 | 4 |
| Weight decreased | 2 | 1 |
| **Musculoskeletal and connective tissue disorders** | | |
| Back pain | 2 | 1 |
| Extrapyramidal disorder | 4 | 1 |

| Body System and MedDRA Term[a] | Percentage of Subjects With Adverse Events* | |
|---|---|---|
| | SEROQUEL XR (n=166) | Placebo (n=172) |
| Pain in extremity | 2 | 1 |
| **Respiratory disorders** | | |
| Nasal congestion | 2 | 0 |

* Events for which SEROQUEL XR incidence was equal to or less than placebo are not listed in the table. Table reports percentage rounded to the nearest integer.

a Patients with multiple events falling under the same preferred term are counted only once in that term.

b The following extrapyramidal events occurred in 1% of patients treated with SEROQUEL XR compared to <1% in placebo: hypersomnia, restless legs syndrome, joint stiffness, muscular weakness, pharyngeal/laryngeal pain and vision blurred.

**Other Adverse Events:** *Weight Gain:* In placebo-controlled MDD and schizophrenia clinical trials, the patients treated with SEROQUEL XR whose weight gain was 0.87 kg (n=1149) compared to 0.31 kg (n=4410) in patients treated with placebo. In a long-term randomized withdrawal MDD trial, patients who completed at least 156 days of SEROQUEL XR treatment (n=196), whose weight gain for patients in SEROQUEL XR 50, 150 and 300 mg/day groups was 1.0 kg, 2.5 kg and 3.0 kg, respectively. In these same patients the percentage of patients experiencing a weight increase of ≥7% by 156 days in SEROQUEL XR 50, 150 and 300 mg/day groups were 13%, 24% and 32%, respectively (see WARNINGS AND PRECAUTIONS). Based on the cumulative acute placebo-controlled clinical trial database, weight gain (based on ≥7% increase in body weight from baseline) was reported in 9.6% in quetiapine-treated patients and 3.0% in placebo-treated patients, which occurs predominantly during the early weeks of treatment in adults (see WARNINGS AND PRECAUTIONS). *Sedation:* There have been uncommon reports (≥0.1% - <1%) of seizures in patients administered quetiapine, although the frequency was no greater than that observed in patients administered placebo in controlled clinical trials (see WARNINGS AND PRECAUTIONS, Neurologic). *Restless Legs Syndrome:* There have been uncommon cases of restless legs syndrome in patients administered quetiapine. *Priapism:* There have been rare reports (≥0.01% - <0.1%) of priapism in patients administered quetiapine. *Somnambulism:* Somnambulism may occur, usually during the first 2 weeks of treatment, which generally resolves with the continued administration of SEROQUEL XR. *Neuroleptic Malignant Syndrome:* As with other antipsychotics, rare cases of neuroleptic malignant syndrome have been reported in patients treated with quetiapine (see WARNINGS AND PRECAUTIONS, Neurologic). *Vital Signs:* As with other antipsychotics with α1-adrenergic blocking activity, SEROQUEL XR may induce postural hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see WARNINGS AND PRECAUTIONS, Cardiovascular). SEROQUEL was associated with a mean baseline to endpoint increase in heart rate of 2.9 beats per minute, compared to 1.4 beats per minute in placebo-treated patients. *Peripheral Edema:* As with other antipsychotics, common cases (≥1% - <10%) of peripheral edema have been reported in patients treated with quetiapine. *Allelic Asthenisia:* As with other antipsychotic agents, uncommon cases of allelic asthenisia have been reported in patients treated with quetiapine. *Akinesia:* There have been common reports of akinesia in patients administered quetiapine. *Hypersensitivity:* Uncommon cases of hypersensitivity including angioedema have been reported. *QTc Changes:* In a 600 mg/day therapeutic study, 0.2% of SEROQUEL XR patients, and no placebo patients, had tachycardia (>120 bpm) at any time during the trials. SEROQUEL XR was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean decrease of 1 beat per minute for placebo. This is consistent with the class of SEROQUEL. This slight tendency to tachycardia may be related to the potential of SEROQUEL XR for inducing orthostatic changes (see WARNINGS AND PRECAUTIONS, Cardiovascular). *Extrapyramidal Symptoms (EPS):* In short-term placebo-controlled monotherapy clinical trials in MDD, the aggregated incidence of EPS was 5.4% for SEROQUEL XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with MDD, the aggregated incidence of EPS was 9.8% for SEROQUEL XR and 2.3% for placebo. In long-term studies of schizophrenia, bipolar disorder and MDD, the aggregated exposure-adjusted incidence of treatment-emergent EPS was similar between quetiapine and placebo. *Dysphagia:* There have been uncommon cases of dysphagia in patients administered quetiapine. *Dysarthria:* There have been uncommon cases of dysarthria in patients administered quetiapine. *Acute Withdrawal (Discontinuation) Symptoms:* In acute placebo-controlled monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 12.1% for quetiapine and 6.7% for placebo. The aggregated incidence of the individual adverse events (e.g., insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability) did not exceed 5.3% in any treatment group and usually resolved 1 week after discontinuation. *Abnormal Dreams and Nightmares:* There have been uncommon cases of abnormal dreams and nightmares in patients administered quetiapine. *Suicide-Related Events:* In three trials of patients with MDD the incidence of suicide-related events was 2.3% (5/144) for quetiapine and 1.3% (1/75) for placebo in patients 10-24 and 0.6% (11/1798) for quetiapine and 0.7% for placebo (7/1054) in patients >25 years of age. *Irritability:* There have been uncommon cases of irritability in patients administered quetiapine. *Increased Appetite:* There have been uncommon cases of increased appetite in patients administered quetiapine. *Abnormal Hematologic and Clinical Chemistry Findings:* As with other antipsychotics, uncommon cases of leucopenia and/or neutropenia have been observed in patients administered quetiapine. Uncommon cases of eosinophilia and thrombocytopenia (platelet count decreased, <100 x 10⁹/L on at least one occasion) have been observed. Based on clinical trial adverse event reports and associated with neuroleptic malignant syndrome, rare cases of elevations in blood creatine phosphokinase have been reported in patients administered quetiapine. Common cases of elevations in serum prolactin levels have been observed (>20 µg/L in males and >30 µg/L in females) (see WARNINGS AND PRECAUTIONS, Hyperprolactinemia). In three-arm SEROQUEL XR placebo-controlled monotherapy clinical trials, among patients with a baseline neutrophil count >1.5 x 10⁹/L, the incidence of at least one occurrence of neutrophil count <1.5 x 10⁹/L was 1.5% in patients treated with SEROQUEL XR and 1.5% for SEROQUEL, compared to 0.8% in placebo-treated patients. In all placebo-controlled monotherapy clinical trials among patients with a baseline neutrophil count >1.5 x 10⁹/L, the incidence of at least one occurrence of neutrophil count <1.5 x 10⁹/L was 1.72% in patients treated with SEROQUEL, compared to 0.73% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count <1.0 x 10⁹/L, among patients with a baseline neutrophil count >1.5 x 10⁹/L, the incidence of at least one occurrence of neutrophil count <1.5 x 10⁹/L was 0.21% in patients treated with SEROQUEL and 0% in placebo-treated patients and the incidence of <1.5 - <1.0 x 10⁹/L was 0.15% in patients treated with SEROQUEL and 0.11% in placebo-treated patients (see WARNINGS AND PRECAUTIONS, Hematologic). Common cases of asymptomatic elevations in serum transaminases (ALT, AST or uncommon cases of >3× normal) have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment (see WARNINGS AND PRECAUTIONS, Hepatic). SEROQUEL treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total $T_4$ and free $T_4$. The reduction in total and free $T_4$ was maximal within the first 2 to 4 weeks of quetiapine treatment, with no further reduction during long-term treatment. There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free $T_4$, irrespective of the duration of treatment. Sporadic decreases in total $T_3$ and reverse $T_3$ were seen only at higher doses. Levels of TBG were unchanged and in general reciprocal increases in FSH were not observed and there was no indication that SEROQUEL causes clinically relevant hypothyroidism (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolic). *Hyperglycemia:* Blood glucose increases in hyperglycemic levels (fasting blood glucose >7.0 mmol/L or a non-fasting blood glucose >11.1 mmol/L on at least one occasion) have been observed commonly (≥1% - <10%) with quetiapine in clinical trials. In short-term (12 weeks duration or less) placebo-controlled clinical trials (3542 treated with quetiapine and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥7.0 mmol/L or a non-fasting blood glucose ≥11.1 mmol/L was 2.5% for quetiapine and 2.1% for placebo. In a 24-week trial (active-controlled), 115 patients treated with SEROQUEL) designed to maintain glycemic status with oral glucose tolerance testing of all patients, at Week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥11.1 mmol/L was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥7.0 mmol/L was 2.6% (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolic). *Cholesterol and Triglyceride Abnormalities:* Very common (≥10%) cases of elevations in serum triglyceride levels (>2.258 mmol/L on at least one occasion) and elevations in total cholesterol (unclear exactly LDL cholesterol) (>6.2064 mmol/L on at least one occasion) have been observed during treatment with quetiapine in clinical trials (see WARNINGS AND PRECAUTIONS, Cardiovascular). Lipid increases should be managed as clinically appropriate. In one 24-week clinical trial, where LDL cholesterol was directly measured as opposed to calculated, there was a slight mean increase in total cholesterol in patients administered SEROQUEL, which was driven by increases in LDL cholesterol. The mean LDL level increased at Week 24 by 10% in patients administered SEROQUEL, which were statistically significant. The total cholesterol/HDL ratio did not change significantly during therapy with SEROQUEL. Furthermore, triglycerides did not increase significantly nor did HDL cholesterol decrease during therapy (see WARNINGS AND PRECAUTIONS, Cardiovascular). *Post-Marketing Adverse Drug Reactions:* During post-marketing experience, neutropenia and/or neutropenia have been reported during SEROQUEL treatment. Resolution of leucopenia and/or neutropenia has followed cessation of therapy with SEROQUEL. Possible risk factors for neutropenia and/or neutropenia include pre-existing low white cell count and history of drug-induced neutropenia and/or neutropenia (see WARNINGS AND PRECAUTIONS, Hematologic). As with some other antipsychotics, hyperglycemia and diabetes mellitus (including exacerbation of pre-existing diabetes, diabetic ketoacidosis and diabetic coma including some fatal cases) in the aggregate have been reported rarely (≥0.01% - <0.1%) during the use of SEROQUEL, sometimes in patients with no reported history of hyperglycemia (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolic). Angioedema reactions have been reported very rarely in post-marketing reports, including a case with a fatal outcome, possibly related to SEROQUEL treatment. The reporting rate of angioedema associated with SEROQUEL use, which is generally accepted to be an underestimate due to underreporting, does not exceed the background incidence rate estimates. Estimates of the background incidence rate (all causes) of severe life-threatening angioedema in the general population range between 80 and 310 cases per million person-years, and the incidence rate of drug-induced angioedema is assumed to be 14 cases per million person-years. In addition, the all-cause fatal anaphylaxis rate is reported to be one per million person-years while drug-induced fatal anaphylaxis is estimated to be 0.3 cases per million person-years. If a patient develops anaphylaxis after treatment with SEROQUEL XR, the drug should be discontinued and an alternative treatment started. Based on post-marketing reports, pancytopenia has been reported rarely.

### Drug Interactions

**Drug-Drug Interactions: The Effect of SEROQUEL XR on Other Drugs:** *Alcohol:* SEROQUEL (quetiapine, immediate-release formulation) potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with psychotic disorders. Alcoholic beverages should be avoided while taking SEROQUEL XR. *Antihypertensive Agents:* Because of its potential for inducing hypotension, SEROQUEL XR may enhance the effects of certain antihypertensive agents. *Levodopa and Dopamine Agonists:* As it exhibits in vitro dopamine antagonism, SEROQUEL XR may antagonize the effects of levodopa and dopamine agonists. *Lithium:* The single dose pharmacokinetics of lithium were not altered when coadministered with SEROQUEL. *Antipsychotics:* SEROQUEL did not induce the hepatic enzymes involved in the metabolism of antipsychotics. *Lorazepam:* SEROQUEL did not affect the steady-state pharmacokinetics of lorazepam. *Divalproex:* Coadministration of SEROQUEL (150 mg bid) and divalproex (500 mg bid) increased the mean oral clearance and the mean maximum plasma concentration of total valproic acid (administered as divalproex) by 11%. These changes were not clinically relevant. **The Effect of Other Drugs on SEROQUEL XR:** *Hepatic Enzyme Inducers:* Concomitant use of SEROQUEL XR with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. In a multiple-dose trial in patients to assess the pharmacokinetics of SEROQUEL given before and during treatment with carbamazepine (a known hepatic enzyme inducer), coadministration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone, although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations were seen, and hence, in each patient, consideration for a higher dose of SEROQUEL XR, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of SEROQUEL XR is 800 mg/day and continued treatment at higher doses should only be considered as a result of careful consideration of the benefit/risk assessment for an individual patient. Coadministration of SEROQUEL and another enhanced enzyme inducer, phenytoin, caused five-fold increases in the clearance of quetiapine. Increased doses of SEROQUEL XR may be required to maintain control of psychotic symptoms in patients coadministered SEROQUEL XR and phenytoin and other hepatic enzyme inducers (e.g., barbiturates, rifampicin, etc.). The dose of SEROQUEL XR may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g., sodium valproate). *CYP 3A4 Inhibitors:* CYP 3A4 is the primary enzyme responsible for cytochrome P450-mediated metabolism of quetiapine. Thus, coadministration of compounds (such as ketoconazole, erythromycin, clarithromycin, diltiazem, verapamil or nefazodone), which inhibit CYP 3A4, may increase the concentration of SEROQUEL XR. In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of SEROQUEL given before and during treatment with ketoconazole, coadministration of ketoconazole resulted in an increase in mean $C_{max}$ and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean $t_{max}$ was unchanged. Due to the potential for an interaction of a similar magnitude in a clinical setting, the dosage of SEROQUEL XR should be reduced during concomitant use of quetiapine and potent CYP 3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors). Special consideration should be given to elderly and debilitated patients. The risk/benefit ratio needs to be considered on an individual basis in all patients. *Divalproex:* Coadministration of SEROQUEL (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine by 17% without changing the mean oral clearance. *Cimetidine:* In a clinical study ascertaining the pharmacokinetics of SEROQUEL following coadministration with cimetidine (a non-specific P450 enzyme inhibitor), no clinically significant interaction was observed. *Thioridazine:* Coadministration of thioridazine (200 mg bid) with SEROQUEL (300 mg bid) increased the clearance of SEROQUEL by 65%. *Fluoxetine, Imipramine, Risperidone and Risperidone:* Fluoxetine (60 mg daily), imipramine (75 mg bid), risperidone (7.5 mg bid) and risperidone (3 mg bid) did not significantly alter the steady-state pharmacokinetics of SEROQUEL. *In patients taking the following antihypertensives:* enalapril, lisinopril, clonidine, dehydralazine, methyldopa, prazosin, terazosin and remifentanil, addition of SEROQUEL XR (150 mg or 300 mg/day) for up to 4 weeks did not appear to have a consistent overall effect on the trough or peak plasma concentrations of the antihypertensive. **Drug-Food Interactions:** SEROQUEL XR can be taken with or without food. **Drug-Herb Interactions:** Interactions with herbal products have not been established. **Drug-Laboratory Interactions:** Interactions with laboratory tests have not been established.

### Overdosage

**For management of suspected drug overdoses, contact your regional Poison Control Centre.**

**Experience:** *Clinical Trials:* One death has been reported in a clinical trial following an overdose of 13,600 mg of quetiapine alone; however, survival has also been reported in acute overdoses of up to 30,000 mg of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events. *Post-Marketing:* In post-marketing experience, there have been cases of coma and death in patients taking a SEROQUEL (quetiapine, immediate-release formulation) overdose. The lowest reported dose associated with coma has been in a patient who took 9000 mg and has a full recovery within 3 days. The lowest reported dose associated with a death was in a patient who took 6000 mg. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension and Syncope). *Symptoms:* In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects (e.g., drowsiness and sedation, tachycardia and hypotension). *Treatment:* There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patient airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Close medical supervision and monitoring should be continued until the patient recovers.

AstraZeneca

Member

Product Monograph is available upon request from AstraZeneca Canada Inc.

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AstraZeneca Canada Inc.
Mississauga, Ontario L4Y 1M4
www.astrazeneca.ca T 1-800-668-6000 F 1-800-250-1909


SEROQUEL XR (quetiapine fumarate extended-release) is indicated for the symptomatic relief of major depressive disorder (MDD) when currently available approved antidepressant drugs have failed either due to lack of efficacy and/or lack of tolerability.

While there is no evidence that the efficacy of SEROQUEL XR is superior to other antidepressants, it provides a treatment option for patients who have failed on previous antidepressant treatments. Clinicians must take into account the safety concerns associated with antipsychotic drugs, a class of drugs to which SEROQUEL XR belongs. Safety concerns of this class include: weight gain, hyperlipidemia, hyperglycaemia, tardive dyskinesia and neuroleptic malignant syndrome (see WARNINGS AND PRECAUTIONS). SEROQUEL XR should only be prescribed in patients with MDD by clinicians who are aware of the importance and are experienced in the early detection and management of the above-mentioned safety issues associated with this class.

Long-term safety of SEROQUEL XR in MDD has not been systematically evaluated. Thus, the physician who elects to use SEROQUEL XR in the treatment of MDD should use SEROQUEL XR for the shortest time that is clinically indicated. When lengthier treatment is indicated, the physician must periodically re-evaluate the long-term usefulness of the drug for the individual patient keeping in mind the long-term risks.

SEROQUEL XR is also indicated for the management of the manifestations of schizophrenia, as monotherapy for the acute management of manic episodes associated with bipolar disorder and as monotherapy for the acute management of depressive episodes associated with bipolar I and bipolar II disorder. Please consult the Product Monograph for complete prescribing information.

SEROQUEL XR (quetiapine fumarate extended-release) is contraindicated in patients with a known hypersensitivity to this medication or any of its ingredients.

During acute MDD therapy with SEROQUEL XR, the most commonly observed adverse events associated with the use of SEROQUEL XR (incidence of at least 5% and an incidence at least 5% higher than that observed with placebo) were as follows: *Adults*: dry mouth (35%), sedation (26%), somnolence (24%), dizziness (14%) and fatigue (7%). *Elderly*: somnolence (33%), dry mouth (20%), headache (19%) and fatigue (6%).

Increases in blood glucose and hyperglycaemia, and occasional reports of diabetes have been observed in clinical trials.

Eye examinations are recommended prior to, or shortly after, initiation of treatment and at 6-month intervals thereafter. Caution should be used in the elderly and those with known hepatic and renal impairment.

**Serious Warnings and Precautions**

**Increased Mortality in Elderly Patients With Dementia**

Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in death rate in the drug-related patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Please consult the Product Monograph for warnings, precautions and adverse events.

Reference: 1. SEROQUEL XR® Product Monograph. AstraZeneca Canada Inc. May 27, 2009.



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See prescribing summary on page