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POSITION PAPER

Access to Newer Medications

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Introduction

There is a growing concern that Canadians who are dependent on public drug programs do not have equal access to emerging new medications for mental disorders, compared with those who have private drug insurance coverage. There are also inequities in public drug plans among the provinces and territories. As pharmacologic treatment is often the best first-line treatment for, or the major treatment component of, severe mental disorders, the Canadian Psychiatric Association (CPA) remains committed to improving the mental health of all Canadians, by ensuring the availability and accessibility of effective and safer medications to meet the mental health needs of the population. This position paper addresses pertinent issues and complexities relating to the drug approval process, cost-effective analysis, and cost-containment strategies, and it provides recommendations on improving accessibility to new medications for mental disorders based on an individual patient's clinical treatment needs.

Background

Social and Economic Burden of Mental Disorders

Mental illness affects Canadians irrespective of age, sex, education, income, and ethnicity, either directly or indirectly, through a family member, friend, or colleague. About 20 per cent of Canadians personally experience a mental illness in their lifetime. Chronic major psychiatric disorders, such as schizophrenia and bipolar disorder (BD) type I, individually affect one per cent of the population and their families. Further, one in four women and one in 10 men can expect to develop a depressive episode.[1] Given these statistics, in 2003, the cost of mental illness in Canada was estimated at $51 billion a year in health care and lost productivity.[2] Pharmacologic treatment remains the most important component in the management of major psychiatric disorders, such as schizophrenia, BD, and severe major depression. Medication treatment is often supported by appropriate psychosocial interventions to regain baseline functioning, productivity, and overall recovery. Despite significant progress in the pharmacologic treatment of

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mental disorders in the last two decades, the burden of mental illness is growing in Canada and worldwide. According to the World Health Organization,[3] psychiatric conditions, such as depression, schizophrenia, BD, and alcohol and drug abuse, are the most important causes of disability, accounting for one-third of years lost owing to disability among adults aged 15 years and older.

Limitations in Current Pharmacotherapy

Several complex factors are involved in translating the evidence-based treatment to individualized optimum treatment of mental illness, and optimum treatment does not always produce an optimal outcome in each patient. The efficacy data generated from randomized controlled trials (RCTs) cannot be generalized to real-world patients because of selection bias (that is, inclusion of selective patients) in clinical trials. The data from a large sample of patients in an RCT may not be clinically useful to select the right treatment of individual patients because of huge interindividual variations in treatment responses and tolerability. There is limited understanding of the wide differences in treatment responsiveness, medication tolerability, clinical outcome, and biologic risk factors for mental illnesses. Currently, there are no clinically or biologically useful methods to predict responders from nonresponders to specific treatments. Several potential predictors (such as clinical, demographic, genetic, endocrine, and proteomic, and neuroimaging markers) of clinical outcomes have not yet been shown to be reliable for routine clinical use.[4] Hence the availability of a wide choice of medications is essential to provide the best treatment possible for the individual patient's response and tolerability to medications.

In recent years, there has been a paradigm shift in treatment approaches for mental disorders that require new, effective, and safe drugs. Emerging evidence suggests that major psychiatric disorders, such as schizophrenia and BD, are neurodevelopmental disorders that commonly manifest during adolescence.[5] Evaluation of new early treatment interventions (such as pharmacological and psychological treatments) focusing on the presymptomatic phase (that is, with a high risk for psychosis and mood disorders) and the prodromal phase (that is, the early symptomatic phase) of these mental disorders are required.[6] There is a growing need for clinically effective and safe preventive treatment of major mental disorders. Although second-generation (atypical) antipsychotics (SGAs) are currently used as a preferred treatment in the early stages of psychotic disorders, younger patients, including children and adolescents, are at the highest risk of developing metabolic complications associated with SGAs.[7] Another limitation of current pharmacotherapy for mental disorder is treatment resistance. For example, in large-scale clinical trials, such as Sequenced Treatment Alternatives to Relieve Depression (commonly referred to as STAR*D), only 20 to 35 per cent achieved remission (a score of less than seven on the 17-item Hamilton Depression Rating Scale), with the first antidepressant (AD) treatment highlighting the ineffectiveness of available treatment for depression.[8] Hence effective medications are required to treat resistant mental disorders. Access to new emerging drugs for treatment-resistant disorders will be crucial in the effective management of major mental disorders in the future.

Prescription Drug Coverage in Canada

In the Canadian health care system, outpatient prescription drugs are excluded from the universal health coverage. About 75 per cent of Canadians have private insurance coverage for prescription drugs and only 25 per cent (seniors, unemployed, and social assistance recipients) are eligible for coverage by the public drug plans.[9] People with severe mental illness are often unemployed and subsisted with social assistance; therefore, the increasing formulary restrictions create a two-tier system for prescription coverage for people with mental illness, which goes against the policy of universal health coverage for all Canadians. Further, not all Canadians currently have equal access to new psychotropic medications; some provinces have made new psychotropic medications more accessible for their residents under the public drug plan than have other provinces.

Drug Approval Process

The drug approval process in Canada involves two stages: first, Health Canada (a federal agency) must certify that new medications are safe and effective for public use based on the evidence from randomized placebo-controlled trials. Second, public drug programs (provincial and territorial government agencies) must decide if the drug could be reimbursed within public drug programs based on the comparative assessment of cost-effectiveness and safety of the drug, compared with existing therapies.[10] Canadians who rely on the public drug plan have access to new medications only after the approval from public drug plans. Private drug insurers decide independently whether a drug approved by Health Canada could be covered by private insurance for their clients.

The publicly funded drug plan ensures that drugs approved by Health Canada are accessible to patients who otherwise could not afford to buy new effective medications, because of loss of income resulting from long-term mental disorders. However, because of limited health care funding, new drugs are added to the formulary listing in the 18 participating publicly funded drug plans in Canada (except Quebec) after

an assessment of cost-effectiveness of the drugs by a Common Drug Review (CDR) process. CDR was established in 2003 by federal, provincial, and territorial ministers of health to provide a single national process for making formulary recommendations. Several Western countries have established a centralized review process, which is considered to be critical for publicly funded drug plans.[11] With the implementation of CDR, the review process became a single national process and duplication of effort in reviewing new medications was eliminated. The transparency of the review process also improved.

As a first step, a review team, consisting of epidemiologists, pharmacists, physicians, health economists, and a librarian, conduct a systematic review of all relevant published and unpublished RCTs, and critically evaluate the manufacturer's pharmacoeconomic evaluation. This report is submitted to the Canadian Expert Drug Advisory Committee (CEDAC). The CEDAC, a committee of 12 members and a chair, including physicians, pharmacists, pharmacologists, and nurses, makes positive or negative recommendations to formulary (public drug plan), based on the assessment of the medications' clinical effectiveness, safety, and cost-effectiveness, compared with existing therapies. Two representatives from the public are also included, as full voting members in CEDAC, to improve the transparency of drug formulary policies.

The provincial drug plans decide whether to list the drug on drug formularies after taking into consideration CEDAC's recommendations, each province's health priorities, available health care funding, and previous formulary decisions. The list of prescription drugs funded through a public drug plan is called a formulary. Each province and territory has its own formulary and the decision to include a drug in a formulary is independently made by each jurisdiction. An expensive new medication may be covered in one province and not in another even if a CDR provided positive recommendations about that medication.

Quebec's Drug Review Process

Quebec has its own drug review process by the Medication Council and thus is not subject to the CDR process. The council meets three times a year and reviews applications for inclusion of drugs on the drug benefit list that were pre-approved by Health Canada. Compared with the CDR process, the Medication Council offers measures to ensure that Quebec pays fair and reasonable prices for medications included in the drug benefit list and drugs approved by the Medication Council should be covered both by the government (Quebec) drug insurance plan as well as by the private plans. The private plans can also provide coverage for drugs not approved by the Medication Council.

Criticisms of the Public Drug Regulatory Process

CDR Recommendations

It was hoped that the creation of the CDR would improve access to new effective medications in a timely fashion under the public drug plan. However, the implementation of CDR has not produced any major changes to improve access to new medications. Although CDR has reduced the time taken to grant approval by public plans from the average wait of 479 days (before 2002) to 316 days (2008), private insurers tend to provide coverage far more rapidly than the public plans.[12] Further, only 16 to 23 per cent of drugs approved by Health Canada as clinically effective and safe from 2004 to 2008 were approved for reimbursement under provincial drug plans.[12] The CDR approves fewer drugs than other developed countries. The CDR approval rate is 52 per cent, compared with 76 per cent in the United Kingdom, 80 per cent in Switzerland, 82 per cent in Sweden, and 58 per cent in France[13] for the same drugs. Because the public drug plan decisions are in agreement with the CDR decisions most (90 per cent) of the time,[14] the CDR's low approval rate may have a negative effect on access to new medications under the public plan. In contrast, private insurers tend to provide coverage for more new drugs than the public drug plans.

Cost-effectiveness Assessment

The estimation of the cost-effectiveness of a drug is mostly based on imperfect evidence. A CDR frequently makes arbitrary decisions about the cost-effectiveness of a drug if there is ambiguity or uncertainty in the evidence. The CEDAC–CDR usually recommends against funding a drug that otherwise would have provided positive recommendations because of the high cost. CDR does not have the mandate to negotiate prices if the drug is expensive. The price negotiations regarding formulary listings take place at the provincial level after the CDR recommendations. Unlike in Australia, drug plans in Canada do not have a national strategy to collectively initiate price negotiation before the CDR process or as part of the CDR process.[15] Having a national strategy on drug pricing negotiations as part of the CDR process may improve the approval rate of newer medications by CDRs and also reduce interprovincial differences in drug plans.

Another limitation is that cost-effectiveness analysis is primarily based on the unit pricing of the new drug without taking into consideration the long-term benefits in terms of compliance, relapse prevention, and rehospitalization. Formulary restrictions for psychiatric medication may not save as much money as other types of medical drugs[16] and formulary restrictions in psychotropic medications may result in increased use

of acute mental health services.[17] Further, the CEDAC uses stringent criteria to evaluate the cost-effectiveness of recent psychotropic drugs. The new drugs should fulfil two criteria to receive positive recommendations: be superior in efficacy and (or) favourable side effect profile, and be cost-effective (comparable cost or cheaper than the existing medications within the class). Based on these criteria, the CEDAC issued negative recommendations for recently introduced atypical antipsychotics in Canada, although these medications have more favourable metabolic and weight gain side effect profile than other approved SGAs and the cost of these drugs is comparable with existing SGAs. This is because there is no clear evidence that these medications offer therapeutic advantage over other SGAs or first-generation antipsychotics (FGAs) and they are not cheaper than the comparative drugs. It is unreasonable to expect that new therapies should be clinically superior and at the same time cheaper than existing therapies for inclusion in a formulary. The price of patented drugs is monitored and regulated in Canada by the Patented Medicines Prices Review Board (PMPRB) so that the prices charged for patented drugs are not excessive, compared with other specified industrialized countries, such as the United Kingdom, Germany, France, Australia, and the United States.[18]

Addressing Issues Related to Cost-containment Strategies

Canadian governments spend more money on prescription drugs than many other Western countries.[18] The average annual growth rate in spending on prescription medication was 10.6 per cent between 1985 and 2005; the annual growth rate in total health expenditure was 6.5 per cent.[19] In 2008, the total drug expenditure was estimated to be $29.8 billion.[20] The increase in drug costs is largely caused by increases in price and use rather than inflation and change in population size or demographics. Canadian governments pay more for generic, patented, and nonpatented drugs than many other Western countries. Concern about rapidly rising prescription drug costs have generated several cost-control strategies to contain growth in spending on drugs. Among the many cost-control strategies, the strategies that limit drug use through formulary exclusion and formulary restriction by limiting coverage to the cheapest drug remain unpopular among physicians. Other strategies, such as generic substitution, reducing overuse by influencing the prescribing behaviour of physicians, and implementing a national strategy for drug coverage, including pricing and purchasing, have greater potentials to reduce spending on prescription drugs. These strategies are discussed in detail in the following sections.

Older Compared With Newer Medications

Policies, such as step therapy, fail-first requirement (that is, a trial with cheaper drugs), or therapeutic substitution (that is, substitution with cheaper drugs within the same therapeutic class), are designed to reduce costs for drug plans but evidence relating to the effectiveness of these approaches regarding psychotropic medication is limited. For instance, although older FGAs, such as perphenazine and haloperidol, are cheaper and can be used successfully, newer SGAs with novel pharmacologic mechanisms, such as clozapine, can provide optimal treatment of symptoms not responsive to, or inadequately treated by, older medications.[21] The newer ADs, with different mechanisms of action and specific advantages, such as faster action than existing medications (for example, agomelatinin and ketamine), are effective in the treatment of depression, given the heterogeneity in the causes and its chronic course.[22,23] Hence the availability of multiple medication options would allow clinicians to provide successful individualized treatment for patients with complex mental disorders; patient and clinical characteristics are important factors in making treatment choices.

Further, the favourable tolerability or side effect profile of newer medications can improve adherence to treatment, which is crucial in preventing relapses and rehospitalization. For example, the three recent major clinical effectiveness trials (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] schizophrenia trial, Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study [CUtLASS], and European First Episode Schizophrenia Trial [EUFEST]) revealed that FGAs (such as perphenazine or haloperidol) were cost-effective for the treatment of schizophrenia, compared with SGAs (for example, olanzapine, risperidone, quetiapine, and clozapine).[24] However, treatment with SGAs has been shown to have a lower risk of tardive dyskinesia and a higher level of patient satisfaction than FGAs.[25] Patient satisfaction with the treatment has a positive effect on compliance and health care outcomes, and also facilitates shared decision making and patient involvement in health care choices. Compared with older tricyclic ADs (TCAs), newer ADs, with less adverse side effects and less drug interactions, can be used safely in patients with depression who have other medical illnesses.[26]

Therapeutic substitution is based on the assumption that medicines in the same therapeutic class are comparable in therapeutic efficacy. However, not all medications within a therapeutic class have the same efficacy and side effects. For example, clozapine is more effective than other medications in the same therapeutic class (SGAs) for treatment-resistant schizophrenia.[20] Some SGAs (that is, aripiprazole and ziprasidone) have low propensity for weight gain or metabolic effects than

other SGAs (that is, olanzapine, clozapine, risperidone, and quetiapine).[27–29] In addition, interindividual variations in treatment responses and tolerability to medications within the same therapeutic class may cause problems in implementing the policy of therapeutic substitution in all patients.

Expensive long-acting newer medications may be cost-effective in the long term. For instance, long-acting and extended release new psychostimulants are clinically recommended for first-line treatment of attention-deficit hyperactivity disorder (ADHD); these medications result in improved school and work performance by improving adherence and reducing abuse potential.[30] Although the clinical and economic effects of ADHD are huge, most of these medications are not covered by all Canadian public plans because of the high cost. Formulary restrictions, such as the need to prove failure with older immediate release medications first, may delay recovery and increase the risk of school failure, impulse control disorder, conduct disorder, and social problems. Similarly, although long-acting injectable atypical antipsychotics are more expensive than the equivalent oral medications and the long-acting injectable typical antipsychotics, these medications have the potential to improve adherence, reduce relapses, and improve functioning and quality of life in some unstable patients.[31]

Generic Drugs Compared With Brand-name Drugs

Generic substitution (that is, substitution of a branded drug with a generic equivalent) is an important cost-containment strategy that could realize substantial savings in prescription costs in the long term for public and private drug plans. Many psychotropic drugs, including ADs and atypical antipsychotics, that are currently in clinical use as first-line treatments are available as generic drugs.[32] Because generic medications are cheaper than their branded counterparts, generic substitution is the norm in public and private drug plans in many countries, including Canada. However, some patient groups, physicians, and drug companies oppose automatic and mandatory generic substitution. Automatic or mandatory generic substitution would allow pharmacists to dispense a generic product for a prescription of branded medicines. Most of the controversy about automatic generic drug substitution originates from the evidence that some generic products are not equivalent to branded drugs in bioavailability and therapeutic efficacy or safety.[33,34] The variations in pharmacokinetics (bioavailability) between a branded drug and its generic counterpart or between two generic drugs may lead to diminished or loss of therapeutic effect. However, there are few studies reporting loss of clinical efficacy in patients with schizophrenia and anxiety disorders whose therapies were switched from a brand-name drug to generic products.[35,36] In the treatment of epilepsy, the substitution of brand-name drugs by generic antiepileptic drugs is generally discouraged because of several reports of loss of seizure control associated with generic drug substitution.[37] Another potential problem related to generic drugs is serious side effects associated with impurities in the manufacturing process. A contaminant in the generic version of L-tryptophan was linked to an outbreak of esonophilia-myalgia syndrome in more than 1,500 people in the United States.[38]

The discrepancy in bioequivalence between generic and brand-name medications has been partly attributed to the limitations in the current requirements for generic drugs. According to the Food and Drug Administration, a generic drug should be identical or bioequivalent to a brand name in dosage form, strength, route of administration, purity, quality, and manufacturing standards. However, bioequivalency data for a generic drug generated from studies involving healthy young volunteers are acceptable to the regulators. Data from healthy people do not take into account the effect of age, sex, and the illness on the pharmacokinetics of a generic drug. Another limitation is that generic requirements do not specify the ratios of active compound and metabolites or inactive gradients (salt or esters). The requirements for generic drugs need to be more rigorous to ensure that generic drugs are identical to brand-name drugs in bioequivalency and therapeutic efficacy and safety. Danish regulations require bioequivalency data both from patients and volunteers.[33]

The main objective of generic substitution is to reduce the increasing cost of prescription drugs and to ensure that effective medications are affordable and accessible to all Canadians. However, Canadians and their drug plans (public and private) seem to pay more for generic drugs than many other Western countries, including the United Kingdom, the United States, Germany, Australia, New Zealand, and the Netherlands. According to the Competition Bureau,[39] if the prices of generic drugs are regulated and based on international comparisons, spending on generic drugs could save up to $800 million a year.

Managing Overuse of New Prescription Drugs

Concern about overuse of drugs is an important factor when considering free availability of expensive drugs. The increase in drug spending caused by increasing use of new drugs is a special concern to policy-makers for publicly funded drug plans. For example, the increase in use of new ADs raises important questions regarding the appropriateness of that use and the role of aggressive marketing by drug companies. However, recent studies suggest that the increasing use of ADs was caused by substantial increases in prescription of

ADs for conditions other than depression (for example, fibromyalgia, migraine, anxiety disorder, and smoking cessation) improved adherence to guidelines, and increased long-term repeat prescription.[40,41] In addition, newer ADs are more tolerable and easier to use than old TCAs and monoamine oxidase inhibitors, which justifies the increased use of newer ADs. In addressing the challenge of overuse of ADs, it is important to note that Canadians with severe recurrent major depression are undertreated and, at the same time, ADs are inappropriately prescribed to people without depression.[40] Given the possibility that overuse of ADs can coexist with undertreatment, the steps taken to minimize overuse should not exacerbate the problem of undertreatment. Previous attempts to reduce overuse, using prior approval restrictions for alternatives, seem to have a significant effect on compliance with ADs.[42] Educational strategies targeting patients and physicians to improve the appropriate use of expensive medications are more appealing than the restrictive approaches. The availability of information will encourage physicians and patients to take shared responsibility in the use of new, expensive medications.

The Current Status of the National Pharmaceutical Strategy

In 2003, the prime minister and premiers signed a health accord to improve access to many health care services, including access to prescription medication.[43] In 2004, the premiers directed their health ministers to develop and implement a national pharmaceutical strategy as a 10-year plan to strengthen health care.[44] The key action items of this national pharmaceutical strategy are to: develop catastrophic drug coverage, a common national drug formulary and national purchasing strategies; accelerate access to breakthrough drugs and nonpatented drugs; enhance evaluation of real-world drug safety and effectiveness; enhance analysis of cost drivers and cost-effectiveness; enhance action to influence the prescribing behaviour of physicians; and, broaden e-prescribing.[44] However, the national strategy has not progressed much since it was launched, especially in the areas of developing a common national formulary for all prescription medications and a nationwide approach to savings in pricing and purchasing. The stated progress as of 2009 is in the implementation of catastrophic drug coverage in some jurisdictions for Canadians who do not meet the criteria for existing public drug plans and who lack private insurance, coverage of expensive drugs for rare diseases, and improving access to breakthrough drugs and (or) nonpatented drugs.[45]

CPA Policy Positions

1. The CPA strongly supports the notion that all Canadians with mental disorders must have access to all effective treatments, including psychopharmacologic treatments that have been recognized as clinically effective by Health Canada.
2. The CPA supports the policy of equity for access to new medications for all Canadians with mental disorders based on individual clinical needs rather than the cost of medication or location (province or territories) or the type of coverage.
3. The CPA opposes policies that undermine the principle that the selection and prescription of appropriate medication for the treatment of a mental disorder is a clinical decision between the treating psychiatrist or physicians and the patient.
4. In principle, the CPA supports the availability of a wide choice of medications that will enable psychiatrists to apply evidence- and individual-based treatment approaches to provide competent care.
5. In the interest of all mental health patients, their families, and their physicians, the CPA requests harmonization of drug formulary policies across the nation to achieve optimal access to modern care and treatment for every Canadian with a mental illness.
6. To ensure affordability and sustainability of public drug plans, the CPA encourages cost-effective approaches to treatment in mental health services without limiting access to new medication. To that effect, it supports evaluation of new creative or innovative pharmacoeconomic models and establishment of a national strategy to reduce the cost of patented and generic drugs (for example, price management, cost sharing strategies, and privatization of public drug plans), and other efforts, such as improved prescribing behaviour by physicians.

Areas for Improvement and Recommendations

1. The CPA recommends that the criteria for drug approval used by the CDR should be balanced between relative clinical effectiveness and cost-effectiveness. Drugs that fulfil one of the two criteria: superior in efficacy and (or) favourable side effect profile than the existing therapies, or cost-effective (comparable cost or cheaper than the existing medications within the class), should be considered for recommendations without restrictions.
2. The CDR recommendations and the formulary decisions for new psychiatric medications should consider the economic and social burden of mental disorders, the availability of effective treatment, or limitations in existing treatment in addition to the evidence on the cost-effectiveness of medications.

3. The CPA suggests that policy-makers consider a national pan-Canadian approach to reduce inequities in drug plans between the provinces as a way to achieve universal access to medications. It strongly supports establishing a common national drug formulary with committed participation of all provinces to ensure that new prescription medications will be available and accessible to all Canadians.
4. In the present CDR process, the onus is on the pharmaceutical industry to prove the cost-effectiveness of new medications. The available data on cost-effectiveness of psychotropic medications are often inadequate, causing uncertainties and ambiguity leading to negative recommendations. Hence there is a need for publicly funded studies to evaluate cost-effectiveness, taking into account the effect of direct costs (that is, unit price) and indirect costs (that is, side effects, disability, relapses, and rehospitalization) related to medication treatment on health care funding.
5. To minimize the overuse of newer medications, the CPA encourages public education and education for mental health professionals by evidence-based clinical practice guidelines and treatment algorithms for mental disorders that include the cost of each treatment. In this regard, the CPA supports the two national initiatives, the National Prescription Drug Utilization Information System (commonly referred to as NPDUIS) and the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS).[46] The main objective of the COMPUS is to provide strategies to help physicians to prescribe the right medication for the right patient at the right time. To ensure the success of these initiatives, the committed participation of all jurisdictions is essential. Public education about appropriate medication prescription is an important strategy to mitigate the effect of aggressive advertising targeting patients and families.
6. The CPA supports the availability of generic drugs with comparable bioequivalency and therapeutic equivalency to that of approved branded drugs. However, it recommends that the policy of generic substitution should be expanded to allow physicians to override generic substitution if it is not effective or safe for an individual patient. The role of the PMPRB needs to be expanded to monitor and regulate the price of generic medications based on international comparisons.

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