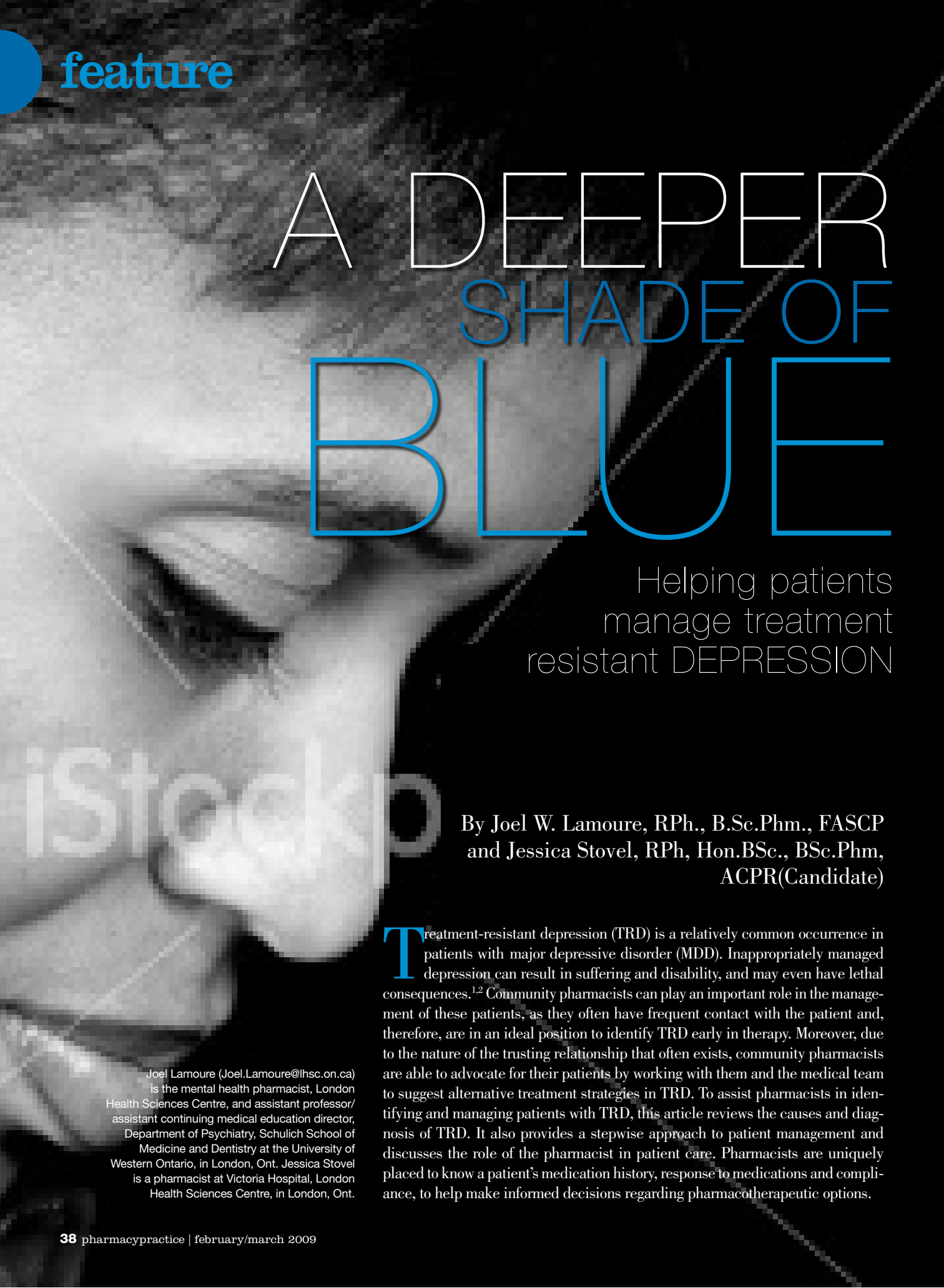


A DEEPER SHADE OF BLUE

Helping patients manage treatment resistant DEPRESSION

By Joel W. Lamoure, RPh., B.Sc.Phm., FASCP and Jessica Stovel, RPh, Hon.BSc., BSc.Phm, ACPR(Candidate)

Treatment-resistant depression (TRD) is a relatively common occurrence in patients with major depressive disorder (MDD). Inappropriately managed depression can result in suffering and disability, and may even have lethal consequences.[1,2] Community pharmacists can play an important role in the management of these patients, as they often have frequent contact with the patient and, therefore, are in an ideal position to identify TRD early in therapy. Moreover, due to the nature of the trusting relationship that often exists, community pharmacists are able to advocate for their patients by working with them and the medical team to suggest alternative treatment strategies in TRD. To assist pharmacists in identifying and managing patients with TRD, this article reviews the causes and diagnosis of TRD. It also provides a stepwise approach to patient management and discusses the role of the pharmacist in patient care. Pharmacists are uniquely placed to know a patient's medication history, response to medications and compliance, to help make informed decisions regarding pharmacotherapeutic options.

Joel Lamoure (Joel.Lamoure@lhsc.on.ca) is the mental health pharmacist, London Health Sciences Centre, and assistant professor/assistant continuing medical education director, Department of Psychiatry, Schulich School of Medicine and Dentistry at the University of Western Ontario, in London, Ont. Jessica Stovel is a pharmacist at Victoria Hospital, London Health Sciences Centre, in London, Ont.

Definition of TRD

TRD has traditionally been defined as an inadequate response to an appropriate course of treatment in a patient meeting criteria for MDD.[1] This definition is controversial, however, as what constitutes an inadequate response can be interpreted in different ways. An inadequate response is commonly characterized as experiencing less than a 50% *reduction in symptoms*, but some define it as a lack of symptom *remission*.[3]

Etiology/diagnosis

Potential causes of TRD are summarized in Table 1. When assessing a patient with TRD, it is imperative to first determine whether the diagnosis is appropriate, as many patients are misdiagnosed initially. Misdiagnosis is often secondary to failure to identify the specific subtype of mood disorder or type of depression (e.g., atypical, psychotic or bipolar depression).[1] It is also important to rule out possible physiological reasons for TRD; hypothyroidism is the number one cause of treatment resistance.[4]

The antidepressant dose and duration of treatment should also be assessed, since only about 40% of patients receive appropriate doses during the first six months of treatment. It is essential to ensure that the dose is maximized to the highest tolerable level for an appropriate duration.[1,2,5] While a six-week trial of the antidepressant appears to be an adequate duration for the majority of patients, some patients may require a longer trial to evaluate efficacy.[1]

It is also important to recognize that a patient's dose may be inadequate secondary to individual variations in drug pharmacokinetics. Specifically, significant interindividual variations occur in the metabolism of antidepressants that are processed by the CYP450 enzyme system. For example, up to 26% of Caucasians may be poor or extensive metabolizers of medications metabolized through CYP2D6 (mainly the 2D6*4 allele).[6]

Since drug dose and duration of treatment are important factors to consider in the diagnosis of TRD, the possibility of nonadherence should also be explored. It has been estimated that at least 20% of TRD is secondary to noncompliance.[1] Finally, alcohol and substance abuse may also contribute to the development of TRD.[2]

table 1

Potential causes of treatment-resistant depression

- Incorrect diagnosis
- Inappropriate medication
- Inadequate dose
- Inadequate trial of antidepressant
- Nonadherence
- Alcohol and/or substance abuse

Consensus criteria for diagnosing TRD are lacking. However, a diagnostic staging scheme commonly used to classify patients with TRD has been proposed by Thase et al:[1,5,7]

- **Stage 1:** Failure of an adequate trial of one class of major antidepressants
- **Stage 2:** Stage I + failure of an adequate trial of a different antidepressant class
- **Stage 3:** Stage II + failure of an adequate trial of a tricyclic antidepressant (TCA)
- **Stage 4:** Stage III + failure of an adequate trial of a monoamine oxidase inhibitor (MAOI)
- **Stage 5:** Stage IV + failure of a course of electroconvulsive therapy (ECT).

Prevalence

The exact prevalence of TRD is difficult to determine because there are no set diagnostic criteria for this condition; therefore, various prevalence estimates have been reported.[1,7] Using data collected in randomized control trials, the prevalence of Stage 1 TRD is estimated to be 50%, with a 35% prevalence for Stage 2.[1,8] The prevalence of TRD also varies according to the treatment setting. The highest prevalence is seen in outpatient psychiatry settings, inpatient acute psychiatric care settings and tertiary care centres.[1]

Management

The optimal strategy for managing TRD has yet to be determined and additional controlled clinical trials are required to identify

the most effective treatment strategy. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, sponsored by the U.S. National Institute of Mental Health, is an ongoing trial that should help to elucidate the best treatment strategies.[5] In the interim, Table 2 outlines an approach to therapy, while a management algorithm suggested by Keller in 2005 is summarized in Figure 1.

DRUG THERAPY

A selective serotonin-reuptake inhibitor (SSRI) is the medication of choice and first course of treatment for most patients with MDD.[1] If a patient fails to completely respond to the first drug after an adequate trial (6–8 weeks), but demonstrates a partial response to the chosen SSRI, then the next strategy is *optimization of the antidepressant dose*.[5,9] While the dose-response curve for SSRIs is fairly flat at the upper end of the recommended therapeutic dosing range, some patients may benefit from higher doses than are typically used.[1]

If no response is achieved with the first agent, and an inadequate dose or duration and/or nonadherence have been ruled out, then *switching to another antidepressant* within the same class is common. If the patient still experiences no improvement in signs and symptoms after an adequate trial (usually 6–8 weeks), switching to another antidepressant from a different class (i.e., with another mechanism of action) is the next step. However, good evidence to support this approach is limited,[1,2,9] and clinical trial data suggest that this approach is effective only 40–60% of the time.[1] The "switch" approach may improve patient compliance and result in fewer side effects, as well as improve response, especially if the reason for failure was nonadherence or adverse effects. It may also be the most cost-effective approach, because the patient is still taking only one medication. Disadvantages of this approach include the possibility of discontinuation syndrome (i.e., antidepressants should be discontinued gradually to avoid withdrawal symptoms), patient reluctance to start a new medication, and the length of time it takes for the new drug to demonstrate a treatment response.[7]

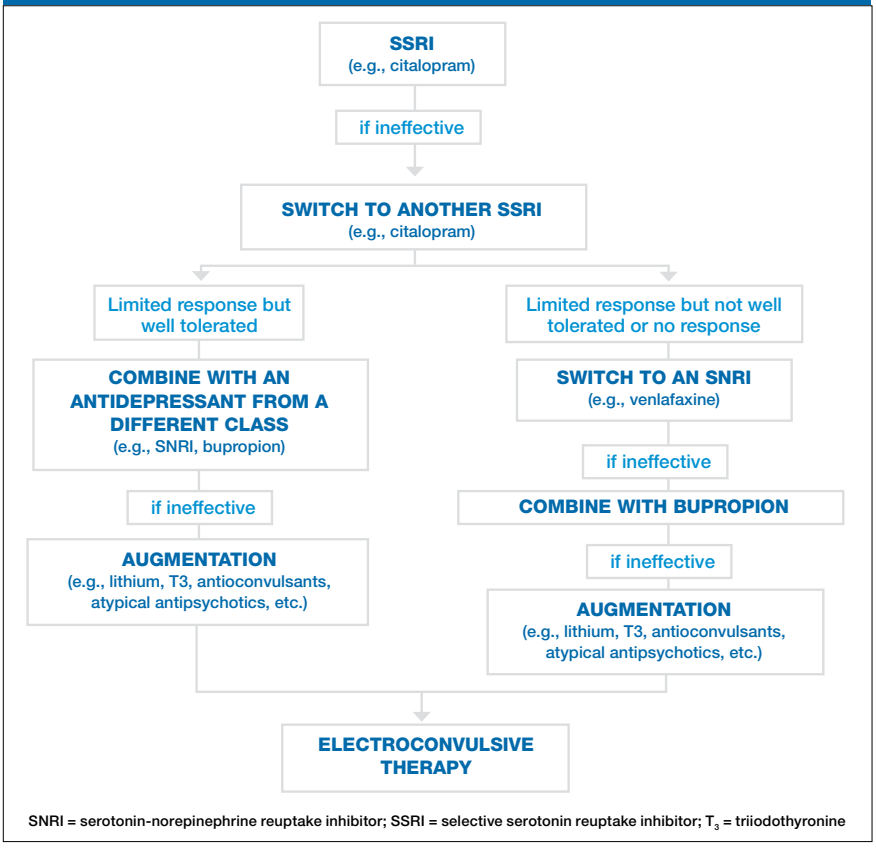
If, on the other hand, the patient with TRD is not tolerating the SSRI antidepressant, then a switch should be made to a serotonin-norepinephrine reuptake inhibitor (SNRI), such as venlafaxine.[7] If the SNRI is still deemed to be ineffective after an adequate trial of six to eight weeks, then combination therapy with bupropion should be tried next.[7]

Although the use of MAOIs has fallen out of favour recently, use of these agents in TRD is still seen, based on evidence to support their use in both early and late TRD. However, the use of MAOIs is still limited by safety concerns, particularly the potential to develop a hypertensive crisis secondary to interactions with common medications, OTCs and foods. Overall, larger and more rigorous randomized controlled trials are required to establish the optimal place of MAOIs in the TRD treatment algorithm.[1]

If a patient has been switched to a different class of antidepressant and is tolerating it, but still has not achieved an adequate response (i.e., symptom remission), an alternate strategy that may be tried is *antidepressant combination therapy*, in which at least two different classes of antidepressants with well-established efficacy are used in order to enhance the effect of the initial antidepressant.[7,9] Common agents used for combination therapy in TRD include noradrenergic and specific serotonergic antidepressants (NaSSAs, e.g., mirtazapine), norepinephrine-dopamine reuptake inhibitors (NDRIs, e.g., bupropion) and SNRIs (e.g., venlafaxine, duloxetine, atomoxetine, desipramine).[1] The most frequent combinations are the addition of a NaSSA to a NDRI agent. Addition of an NDRI to an SNRI, or NDRI to an SSRI are also common strategies.[10] The advantages of combination therapy include avoidance of an antidepressant discontinuation syndrome, and a rapid onset of action due to continuation of the initial antidepressant that produced a partial response. Disadvantages include increased cost to the patient, possible decreased compliance due to use of multiple agents and the increased potential for drug-drug interactions.[7]

Augmentation is the next most common step in patients who still experience signs and symptoms of depression despite increasing the dose of antidepressant, switching antidepressants, and/or trying a combination of antidepressants. Augmentation consists of the addition of a non-antidepressant agent, with the intention

Figure 1 Algorithm for managing treatment-resistant depression[7]



SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; T_3 = triiodothyronine

to pharmacologically or physiologically enhance the effect of the antidepressant. A wide variety of agents can be used to augment the efficacy of antidepressants in TRD. The most common augmentation agents are as follows:[1]

- mood stabilizers (e.g., lithium, lamotrigine, divalproex sodium, carbamazepine)
- miscellaneous agents (e.g., triiodothyronine [T_3], pindolol, atypical antipsychotics, moda-finil, anticonvulsants and dopaminergic agents [such as psychostimulants, bromocriptine, pergolide, ropinirole, pramipexole], benzodiazepines, estrogen, testosterone, inositol, opiates, folates, antiglucocorticoids).

The augmenting agents with the most evidence to support their use are lithium, T_3 and atypical antipsychotics. Given that atypical antipsychotics antagonize the effects of serotonin (which makes them beneficial for the negative symptoms of schizophrenia), augmentation of the initial antidepressant with an atypical antipsychotic makes clinical sense. Augmentation of bupropion with an atypical antipsychotic is also frequently practised, but randomized controlled trials to support this combination are lacking.[10] Augmentation of the initial agent(s) with buspirone and pindolol has also been tested, but findings are conflicting and additional studies are required.[3] While available studies demonstrate that these augmentation strategies are promising, there is still a lack of adequately powered, double-blind, placebo-controlled trials in patient populations with well-defined TRD.[1]

The advantages of the augmentation strategy include lack of an antidepressant discontinuation syndrome since the antidepressant remains active in therapy, since it produced an initial, albeit inadequate, response. Disadvantages include the increased potential for drug interactions, side effects and noncompliance, as well as increased cost to the patient.[7]

NONPHARMACOLOGICAL THERAPY

In addition to the pharmacological strategies discussed above, six main nonpharmacological approaches are used in TRD: ECT, vagus nerve stimulation, transcranial magnetic stimulation, deep brain stimulation, magnetic seizure therapy and cognitive behavioural therapy. Of these, ECT is the best studied and has been shown to be the single most effective treatment for advanced TRD. Meta-analyses conclude that ECT is more effective than antidepressants (e.g., SSRIs, SNRIs, MAOIs) in the treatment of TRD. The few trials that have directly compared ECT to pharmacological therapy have also found higher response rates with ECT. Larger controlled studies are required to evaluate the efficacy of other nonpharmacological approaches.[1]

The pharmacist's role

Pharmacists can play an essential role in the management of patients with TRD. Screening of all medications in the patient's profile can ensure that potential drug interactions are detected and prevented. Pharmacists can ask patients about their goals of pharmacotherapy and whether they are having any untoward effects. When drug side effects occur, pharmacists can help manage them by working with patients and the medical team. Perhaps even more importantly, pharmacists can provide close and consistent patient follow-up, and proactively prevent drug-related problems.

Pharmacists should also ensure that the chosen pharmacotherapy is beneficial. A mood diary is one tool that can be used to help determine response to medications. This very powerful tool also serves to empower patients. Patients chart twice daily on a calendar, rating their mood on a scale of 1 to 10, where 1 is "very depressed" and 10 is "not depressed at all." They can bring this diary when they visit their pharmacist, physician or any member of the healthcare team. Several variants of the mood diary are available to patients on the Internet. In addition to recommending a mood diary, pharmacists can refer patients to support groups and provide additional resources in the form of written pamphlets or reliable websites (Table 3). pp

References and Table 3 are available at www.pharmacygateway.ca (Go to Publication Archives, *Pharmacy Practice*, February/March 2009, A Deeper Shade of Blue).

table 3

Patient resources on depression and antidepressants

DRUGS.COM: WWW.DRUGS.COM
Excellent source of information regarding medications (e.g., side effects, drug interactions, dosing) for patients.
CANADIAN MENTAL HEALTH ASSOCIATION: WWW.CMHA.CA
Nationwide voluntary association that provides information to patients on a variety of mental health issues. Designed to promote mental health, resilience and recovery through advocacy, education and research.
MOOD DISORDERS SOCIETY OF CANADA: WWW.MOODDISORDERSCANADA.CA
National, non-profit organization that aims to improve the quality of life for patients with depression and other related disorders. Site includes an online discussion group and an extensive list of national and provincial resources.
LIFE MD.COM: WWW.DEPRESSIONCANADA.COM
Canadian website developed by healthcare professionals to provide readers with general health information. Contains an excellent section on depression. Also aims to help people evaluate medical information in the news.
MOODS MAGAZINE: WWW.MOODSMAG.COM
Quarterly Canadian publication for patients with mood disorders. Includes information, self-tests and an "ask the pharmacist" section.
MENTAL HELP.NET: WWW.MENTALHELP.NET
An excellent website providing a comprehensive overview of different types of mental health disorders. Lists many different resources, including news, book reviews and information on self-help groups.
CENTRE FOR SUICIDE PREVENTION: WWW.SUICIDEINFO.CA
Alberta-based organization that offers a library and resource centre with information on suicide, as well as suicide prevention training. Also includes an extensive list of crisis centres and suicide hotlines across Canada.
MOOD DISORDERS CENTRE OF EXCELLENCE: WWW.VCH.CA/MOOD
University of British Columbia-based centre that provides innovative programs of care. Also conducts clinical studies on mood disorder causes and treatments.
ALL ABOUT DEPRESSION: WWW.ALLABOUTDEPRESSION.COM
Comprehensive online resource that provides accurate, current and relevant information about depression. Also includes self-tests and a discussion board.

References

1. Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psychiatry 2007;68(Suppl 8):17-25. **2.** Keks NA, Burrows GD, Copolov DL, et al. Beyond the evidence: is there a place for antidepressant combinations in the pharmacotherapy of depression? Med J Aust 2007;186(3):142-4. **3.** Carvalho AF, Cavalcante JL, Castelo MS, et al. Augmentation strategies for treatment-resistant depression: a literature review. J Clin Pharm Ther 2007;32:415-28. **4.** Rosenbaum JF, Covino JM. Treatment-resistant depression: diagnostic strategies and current treatment methods. Medscape Pharmacists 2006 (June). www.medscape.com/viewarticle/537389 (accessed December 9, 2008). **5.** Sourey D, Papakostas GI, Trivedi MH. Treatment-resistant depression. J Clin Psychiatry 2006;67(Suppl 6):16-22. **6.** Bradford L. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics 2002;3:229-43. **7.** Keller MB. Issues in treatment-resistant depression. J Clin Psychiatry 2005;66(Suppl 8):5-12. **8.** Antai-Otong D. The art of prescribing. Monotherapy antidepressant: a thing of the past? Implications for the treatment of major depressive disorder. Perspect Psychiatr Care 2007;43(3):142-5. **9.** Triezenberg D, Vachon D, Helmen J, et al. Clinical inquiries: how should you manage a depressed patient unresponsive to an SSRI? J Fam Pract 2006;55:1081-2, 1087. **10.** Antonuccio D, Yury C, Valenstein M, et al. Common augmentation strategies for depression: findings show lack of evidence. Psychiatric Times 2008;25(3). www.psychiatrictimes.com/depression/article/10168/1147696?pageNumber=2 (accessed December 9, 2008).