OBJECTIVE

Alberta clinicians have the skills and tools to assess, diagnose, treat and manage depression in patients with multiple sclerosis (MS) within primary care.

TARGET POPULATION

Adults 18 years of age and older

EXCLUSIONS

Children less than 18 years of age

RECOMMENDATIONS

> **PRACTICE POINT**
>
> *Be aware that depression is two to three times more common in MS patients than in the general population and can go undetected. Be aware that the suicide rate in people with MS is approximately twice that of the general population. Therefore it is important to be vigilant for depression in patients with MS.*

X DO NOT formally screen each patient for depression (i.e., with depression assessment tools).

✓ If depression is suspected, consider inquiring about mood, anhedonia, irritability and suicidal thoughts.

✓ Perform a more detailed clinical assessment if depression is suspected.

- A depression screening tool can be used to inform clinical diagnosis, but should not be the only source used.
  - The following tools are suggested:
    - PHQ-9 (http://tinyurl.com/http-tinyurl-com-PHQ-9) – a short, easy to use, well known and common tool in the public domain, or
    - Another preferred depression screening tool, or
    - One of the screening tool options listed in Appendix A

Note: The tool selected can provide a baseline measure of depression and serve to assess treatment progress.

DIAGNOSIS

✓ Diagnose depression in the MS patient as per usual process for diagnosing depression.

X DO NOT formally screen every patient taking interferon β even though in the past it has been implicated as a cause of depression – the same principles of assessment should apply in this group of patients.

DIFFERENTIAL DIAGNOSIS

- ✓ Rule out other medical causes of symptoms or consider other conditions that might be presenting as symptoms of depression, e.g., thyroid disease, vitamin B-12 deficiency, an infection causing accentuated MS fatigue (e.g., urinary tract infection [UTI]).

> **PRACTICE POINT**
>
> *Don't be distracted by the diversity of symptoms present among patients with MS. This could result in missing less obvious clinical signs such as those associated with thyroid dysfunction.*

TREATMENT

GENERAL

> **PRACTICE POINT**
>
> *Depression in MS often occurs at emotionally salient times in the disease course and is sometimes intermixed with issues of adjustment and loss. Such issues can be important, but the principles of diagnosis and treatment remain the same irrespective of the apparent root cause of depression.*

- ✓ Admit patients at risk for suicide to hospital for their protection and safety.
- ✓ Closely monitor patients on antidepressants with a personal or family history of bipolar disorder as antidepressants can trigger manic, hypomanic or mixed episodes.
- ✓ Individualize all treatment plans.
- ✓ Consider a combination of medication and non-pharmacological treatment approaches based on patient circumstances and preferences.
- ✓ Actively follow-up mild/brief episodes of depression that may not require immediate or any treatment, and re-evaluate for any change and/or need for treatment.

PHARMACOTHERAPY

- ✓ Consider all antidepressants as treatment options for patients with MS. See Table 1 in Appendix B for commonly used antidepressants for patients with MS.
- ✓ Consider the side effects of specific antidepressants and the patient's symptoms to avoid making the patient's symptoms worse (e.g., strongly anticholinergic medications such as the tricyclic antidepressants and paroxetine may interfere with cognitive function and may accentuate fatigue).
- ✓ Consider any drug interactions with all other medications prescribed for the patient.
    - MS-specific medications are not generally more problematic with respect to drug interactions with certain anti-depressants. See Table 2 in Appendix B for common MS medications and considerations if prescribing an antidepressant.

- ✓ Manage depression as usual for patients taking interferon β.
- ✓ Discuss antidepressant options with patient. Decision-making should be shared between patient and provider.
- ✓ Ask about recreational drug and alcohol use as it may affect antidepressant effectiveness and adherence.

NON-PHARMACOTHERAPY

> **PRACTICE POINT**
>
> *Primary care providers should inquire about cognitive behavioural therapy (CBT) and other mental health services within their own PCN if applicable.*
>
> *Many PCNs have excellent resources for patients.*

- ✓ Recommend cognitive behavioural therapy (CBT) if available (see Appendix C for resources in Alberta).
  - CBT can be provided in-person, by telephone or self-directed (web-based) approach.
- ✓ Provide other support options if CBT is not available, e.g., coping and management skills, and psychosocial support. Resources can be found at:
  - https://beta.mssociety.ca/living-with-ms
  - http://www.nationalmssociety.org/Living-Well-With-MS
- ✓ Offer patients other options if available:
  - Self-help books/manuals in general or specific for MS patients with depression
  - Group or individual therapy (see Appendix D for counselling services)
- ✓ Recommend exercise for some patients to prevent or reduce depressive symptoms but not as a primary or sole option for treatment.
  - If used, implement an exercise regimen carefully to avoid overheating and/or over-exertion that can temporarily exacerbate some MS symptoms.

MANAGEMENT

FOLLOW-UP

- ✓ Follow-up as per any patient with depression and a chronic condition.
- ✓ Designate one physician (primary care or specialist) to manage the patient's depression who will:
  - Clearly communicate with the patient/caregiver and all physicians involved with the care of this patient, that he/she is responsible for managing the depression.

- Ensure regular follow-up occurs to review the treatment plan and revise as necessary until remission is achieved.
- Continue to follow the patient even if the patient is referred to a psychiatrist, psychologist, mental health worker and/or program to ensure the patient is not lost to follow-up and/or not regressing, deteriorating or isolated as a result of their depression.

PRACTICE POINT

Depression relapse is more common in MS than in the general population and MS patients who decide to discontinue their prescribed medication without supervision may regress very quickly.

IMPLEMENTATION CONSIDERATIONS

- Identify patients with MS in physician practice.
- Community neurologists identifying depression in their MS patients can provide/attach the TOP CPG with the consult notes to the primary care physician.
- Primary care physicians who have patients with MS might explore options for a notation or flag, regarding possible depression risk with a link to the CPG, within the patient's medical record.

BACKGROUND

GENERAL PRINCIPLES FOR ADDRESSING DEPRESSION IN MS

- Depression is prevalent in the MS population.
- It is not necessary to screen every patient with MS for depression.
- If depression is suspected a screening tool can be used to help inform diagnosis and monitor outcomes.
- Once a diagnosis of depression is made, patients should be treated and managed as any patient with depression.
- Treatments should be individualized and can include pharmacotherapy, non-pharmacotherapy, non-pharmacologic therapies or a combination of both.
- Patients require close and ongoing follow-up.

While it is difficult to separate the direct effects of MS upon a patient's mood from the non-specific effects of MS as a chronic illness, it is well established that the rate of major depression among people with MS is higher compared with the general population and individuals with most other chronic conditions. Annual prevalence rates up to 20% have been reported and it is not uncommon for reported lifetime prevalence rates to be as high as 50%.[1,2,3] Many studies report prevalence

based on patients attending MS clinics or listed on health registries suggesting that the prevalence of depression in patients with MS may be overestimated. However, in a population-based study of 115,071 adults with 322 individuals having MS, it was demonstrated that the 12 month prevalence of depression in those individuals with MS was 25.7% compared with 8.9% for those without MS.[4]

Given this prevalence, it is important for primary and secondary care providers to be aware of and appropriately detect depression in their patients with MS and ensure it is treated. It is common for depression to be overlooked with the multiple effects and complexity of the MS itself.

ASSESSMENT

There are a variety of measures used to diagnose and quantify the severity of depression among patients with MS with little to no consensus on the best measure to use. As well, because these measures were designed for use in the general psychiatric population many include somatic symptoms; and since somatic symptoms are common in MS, depression may be overestimated. With MS and the diversity of symptoms there is also a risk of "diagnostic overshadowing" that is, assuming that medical issues are a result of the MS.

For newly diagnosed MS there may be an adjustment disorder, but when a patient presents with sufficient symptoms to diagnose a depressive disorder, they should be managed as such. The distinction between a depressive disorder and an adjustment disorder is the severity, persistence and impact of the symptoms, not in a judgement about etiology. In the past the tendency was to try to separate those with endogenous depression versus "situational" depression as a response to life events. However, the current approach is more of a biopsychosocial blend whereby the clinician identifies the "symptoms picture" and addresses the issues for that individual patient.

There are a limited number of population-based studies evaluating prevalence of mental comorbidity in MS. However, one study used administrative health data to identify patients with MS and a matched general population cohort. The age-standardized prevalence of all mental comorbidities was higher in the MS than in the general population: depression (31.7% vs. 20.5%), anxiety (35.6% vs.29.6%), and bipolar disorder (5.83% vs. 3.45%), except for schizophrenia (0.93% vs. 0.93%).[5]

ROUTINE SCREENING

Screening has frequently been proposed as a strategy for detection of depression in MS. In one study, a minimal impact of screening was found, even when coupled with rapid responsive and evidence-based depression care.[6] Other guidelines recommend that screening be part of clinical assessment and routine care for all MS patients using typical screening measures to identify depression such as the Beck Depression Inventory, using a threshold of 13 for positive screens.[7] However, the evidence to support this recommendation is not strong.

Screening interventions are typically defined as and oriented toward early detection. In MS, depressive symptoms are often characterized by a persistent burden of depressive symptoms in a substantial proportion of patients. Therefore it is more effective to focus less on formal screening of all MS patients and more on improving long-term clinical management.[8] Instead of formal screening with a scale, clinicians can ask all MS patients two questions about 1.depressive mood e.g., is the patient feeling sad, hopeless etc. and 2.anhedonia e.g., is the patient experiencing little to no

pleasure from previously pleasurable experiences or things. If the answer is 'yes' to both, the probability of depression is 99%. If the answer is 'no' to both, the probability of depression is less than 2%.[9]

Brief assessment instruments are valuable for contributing to the clinical assessment and providing a baseline to measure improvements during management of major depression in MS. However, such instruments have rarely been validated against a gold-standard diagnostic interview in MS populations. One study[10] evaluated the performance of several assessment instruments: Patient Health Questionnaire (PHQ)-9, PHQ-2, Center for Epidemiologic Studies Depression rating scale (CES-D), and Hospital Anxiety and Depression Scale (HADS-D) in relation to the Structured Clinical Interview for DSM-IV (SCID). All of the instrument scales performed well, each having an area under the ROC > 90%. The PHQ-9 had 95% sensitivity and 88.3% specificity when scored with a cut-point of 11. This cut-point achieved a 56% positive predictive value for major depression. While all of the scales performed well in terms of their sensitivity and specificity, the availability of the PHQ-9 in the public domain and its brevity favours its use. Another study evaluated psychometric properties of the Patient Health Questionnaire-9 (PHQ-9), the Center for Epidemiological Studies Depression Scale-10 (CESD-10), and the 8-item PROMIS Depression Short Form (PROMIS-D-8; 8b short form) in a sample of individuals living with MS. Overall, scores on all 3 scales demonstrated essential uni-dimensionality and had acceptable interim reliability and convergent/discriminant validity. Any of these scales can be used effectively to measure depressive symptoms in individuals with MS. The PHQ-9 offers validated cut-off scores for diagnosing clinical depression. The PROMIS-D-8 measure minimizes the impact of somatic features on the assessment of depression and allows for flexible administration, including Computerize Adaptive Testing (CAT). The CESD-10 measures two aspects of depression, depressed mood and lack of positive affect, while still providing an interpretable total score.[11] Additional scales with the highest profile could be considered as an alternate to PHQ-9.

DIAGNOSIS

Clinicians should be familiar with the DSM-5 criteria for depression, and remember that fatigue, hypersomnia and cognitive dysfunction in MS may confound the interpretation of these diagnostic criteria.[9] Further, clinicians should be aware that patients with MS have greater risk of anxiety, bipolarity and obsessive-compulsive behaviour. Patients with MS who have already been diagnosed with depression may also develop other less common, but equally concerning psychiatric symptoms. Clinicians should be alert to the risk of suicide in patients with MS and for those patients with moderate to severe depression, suicide ideation must be assessed. There is no evidence that inquiring about suicidality increases the risk of suicide. Depression should be suspected when MS patients report a degree of disability not in keeping with their physical signs. The presence of intensified fatigue in MS should alert clinicians to the possibility of depression. Depression may influence cognitive performance, but also influences a patient's interpretation of his/her cognitive dysfunction. Patients with complaints of memory loss should be assessed for depression.[9] Patients who meet screening thresholds for depression, or who endorse any positive responses to suicide inquiries, should be actively assessed for severity and quality of depression, and considered for follow-up on treatment recommendations.[7]

The significance of suicide should not be overlooked when assessing MS patients for depression. A systematic review of the literature was conducted to determine the potential association between

MS and suicidal behavior. A total of 12 articles from peer-reviewed journals were considered and selected for this review. Most studies indicate that there is a higher suicide rate in patients with MS compared to the general population. In addition, and suicide was associated with several risk factors: Depression severity, social isolation, younger age, progressive disease subtype, lower income, earlier disease course, higher levels of physical disability, and not driving. Clinicians should be aware that suicidality may occur with higher frequency in MS patients and available data suggest that the risk of self-harm is higher than expected in MS patients.[12]

Some people with MS experience pseudobulbar affect, which is a disturbance of affective expression. People with this syndrome may cry uncontrollably with minor, or no, provocation. This symptom is not in itself indicative of depression, which is characterised by a persistent depression of subjectively-experienced mood.

TREATMENT

Treatment should be individualized and can include pharmacotherapy, non-pharmacologic therapies or a combination of both depending upon the patient's circumstances and preferences. Current evidence suggests that both pharmacotherapy and certain psychotherapies are effective for treating depressive disorders among patients with MS. The Goldman Consensus Group strongly recommends that treatment modalities should be combined in an integrated biopsychosocial treatment plan whenever possible and ongoing follow-up of the treatment plan is necessary until depressive symptoms are eradicated.[7]

Other treatment considerations for patients with MS and depression include assessing treatment adherence at every visit. Also inquire about alcohol and drug consumption as these behaviours may influence treatment and adherence to treatment.[9]

Because bipolar disorder is markedly elevated in MS (about twice that in the general population),[5] it is important to ask patients about suicide ideation, and monitor for hypomanic and manic symptoms while patients at risk of bipolar disorder are being treated with antidepressant medications.[13]

PHARMACOTHERAPY

There are no evidence-based guidelines to treat patients with MS who present with depression. The choice of treatment depends upon the efficacy and tolerance of the drugs used to treat depression in the general population.[9] Use of antidepressants for depressive disorders in the MS population should strongly be considered.

Although the literature of treatment studies is small, positive outcomes are generally reported. In addition to a few uncontrolled studies, three controlled trials of antidepressant medication for the treatment of depressive disorders have been published. These studies evaluated desipramine, sertraline, and paroxetine, respectively. One meta-analysis has confirmed the positive impact of antidepressant treatment in MS when data from all three studies are combined,[14] but another Cochran review by Koch et al.,[15] failed to confirm this.

Because of the somatic effects of MS, care must be taken to avoid prescribing antidepressants with significant sedating or anticholinergic side effects for those patients with fatigue, orthostatic hypotension, balance, cognitive issues, and bladder problems.[13] Drug treatment with tricyclic

antidepressants, serotonin reuptake inhibitors, noradrenalin reuptake inhibitors, monoamine oxidase inhibitors (MAOIs) have been recommended.[16] However, selective serotonin receptor reuptake inhibitors may be preferred over tricyclic antidepressants because of the common side effects of tricyclics such as a worsening of drowsiness, fatigue, decreased cognitive performance.

MD Drugs – Depression as an Adverse Effect

Interferon-*β*

The drug monograph states that there are risks associated with use of interferon-β1a (subcutaneous and intramuscular) and1b (subcutaneous) for MS patients with depression and/or a history of depression. However, the evidence is inconclusive. Some studies suggest that severe depression and suicide attempts occurred in MS patients treated with interferon-β, and who had no prior psychiatric history, while other studies found no evidence that interferon-β alone causes or exacerbates depression.[17,18] Nonetheless, irrespective of its role as a possible cause of depression in patients, it is necessary to be attentive to depression in patients treated with interferon-β and, if necessary, appropriate anti-depressant treatment.[19]

The glatiramer acetate drug monograph also specifies that depression is an adverse effect. Currently there are no data on the characteristics, prevalence or risk factors for depression in patients using glatiramer acetate. Overall, the risk of depression from glatiramer acetate appears to be no higher than interferon-β and the risk is minimal in both drugs.[4] However, as with interferon-β, it is prudent to be aware of patients using glatiramer acetate and/or show signs of depression, and treat them accordingly.

A retrospective analysis on depression data from the phase III SENTINEL study on natalizumab indicated that a significant number of patients who entered the trial without depression developed a positive score for depression during the trial.[20] However, a more recent phase IV study analyzing fatigue in patients treated with natalizumab showed better scores for depression among treated patients.[21] The drug monograph indicates depression is a potential adverse effect.

Fingolimod (Gilenya): Fewer than 5% of patients using fingolimod develop depression[22] and depression is not among the 15 most common listed side effects of the drug. Studies analyzing fingolimod's adverse events found no significant differences in development or worsening of depression.[23] The drug monograph however indicates depression is a potential adverse effect.

MS Drugs and Anti-Depressant Interactions

Many antidepressants have the ability to cause corrected QT interval (QTc) prolongation, a potential risk factor for ventricular arrythmias. Citalopram and escitalopram are especially likely to affect the QTc. Many QTc prolonging drugs can be used in combination with MS medications. The manufacturer states that if this is necessary, ECG should be monitored at baseline, after treatment administration and routinely (e.g., annually or as guided by overall risk) during co-administration, and after any dose increase. QTc-prolonging drugs should not be prescribed to anyone with a QT>440 ms (female) or 420 ms (male). Further, QTc should not ever exceed 500 ms during titration with these drugs; and clinicians should be aware of and avoid interactions that result in increased exposure to either agent see http://crediblemeds.org/healthcare-providers/professionalfaq/.

When initiating fingolimod, cardiac monitoring is performed since there is a risk of bradycardia, bradyarrythmia, sinus bradycardia and atrioventricular block. However, one study found 35 patients out of 906 already on SNRIs (duloxetine and venlafaxine) and 21 were on duloxetine when they were given their first dose of fingolimod. About one third of the study population had other medical conditions and a significant number of subjects (136/906, 15%) were treated with drugs that may influence heart rate and conduction. Importantly, the use of many medications which can cause bradycardia or influence cardiac conduction, including beta-blockers or anti-psychotic drugs, was not associated with cardiac adverse events.[24]

Therefore, for patients with an otherwise normal range QTc who are taking fingolimod, antidepressants can be safely prescribed provided the patient's QTc is monitored in the first month of starting an antidepressant but after the first month any risk of increased QTc is very low so monitoring QTc less frequently is acceptable i.e. a frequency of monitoring guided by the overall risk.

NON-PHARMACOTHERAPY

COGNITIVE BEHAVIOURAL THERAPY (CBT)

There is some evidence that patients with MS and depression respond favourably to psychotherapy-particularly those approaches that focus on active coping skills e.g., cognitive behavioural therapy (CBT). The Mohr study found that group CBT (and sertraline) out performed expressive-supportive therapy.[25]

Treating depression with CBT involves patient and provider interaction that is focused on developing skills needed to identify and reassess the negative thoughts that impact feelings and behaviours.[26] CBT can be used to address the impact of poor coping styles on depression in MS.[27] Patients who use coping styles that are emotion-focused primarily adjust to their situation but in negative ways, seeking to diminish negative emotions for example through avoidance, smoking, drinking or self-medication.[28-30] CBT can be used to help the patient adopt more positive problem-focused coping styles.[31] CBT techniques can also be used to improve the patient's wellbeing and lessen their perceived disease burden.[28,32,33]

Traditional in-person, therapist-led CBT is most effective if it is accessible. Telephone-delivered CBT-is not as effective as in-person but beneficial for patients living in remote areas and/or are immobile.[25] Self-assisted CBT such as computer-aided CBT is another option that may be effective for some patients but can also be physically challenging and may increase feelings of social isolation [34] Generally, on-line CBT interventions (e.g., MoodGym) are more effective if combined with in-person therapist contact.[35]

A systematic review[36] identified seven eligible studies (n = 433), which evaluated the effect on depression of CBT delivered individually (three studies), in a group (three studies) and by computer (one study). The authors concluded that CBT can be an effective treatment for depression in MS but further research should explore optimal durations and modalities of treatment for patients with different characteristics. For example, cognitive deficits that occur in MS may mean that more repetition is required during the didactic and skill-building components of this therapy.

For individuals with MS, a 16-week program of individual telephone administered CBT (T-CBT) might be effective and considered for treating depressive symptoms. Although current existing guidelines

suggest that there insufficient evidence to support or refute the efficacy and use of individual in-person CBT, individual in-person CBT plus relaxation training, or CBT-based group therapy for depressive symptoms,[37] it is important to note that criteria used to assess the evidence quality can be very rigid. As a result it is possible that effective and/or helpful approaches may not be recommended in guidelines because the studies didn't meet the criteria for inclusion.

Coping Strategies and Management Skills

Although CBT has been most studied, other approaches might also be useful such as generic coping skills and management skills rather than insight-oriented therapies.

A meta-analysis found that psychotherapies emphasizing coping strategies are more effective than those focusing on insight.[13] Coping strategies include obtaining information, finding ways to accommodate symptoms, maximizing general health through lifestyle interventions, setting goals and solving problems. Emotion focused strategies are not usually viewed as being as effective.

Exercise

One systematic[38] was conducted to explore the effects of exercise on depressive symptoms in patients with multiple sclerosis (MS), as well as apply meta-analytical procedures to the results. Fifteen randomized controlled trial studies were identified including a total of 331 exercising subjects and 260 controls. The average Physiotherapy Evidence Database (PEDro) score was 5.6 ± 1.3 points. Only one study applied depressive symptoms as the primary outcome. Four studies showed positive effects of exercise on depressive symptoms. An in-depth analysis of the studies revealed that the baseline level of depressive symptoms, patient disability level, a choice of depression instrument and exercise intensity may influence the results. The meta-analysis included 12 studies reflecting a total of 476 subjects. The standardized mean difference across studies was g = -0.37, 95% confidence interval (-0.56; -0.17), and the null hypothesis of homogeneity within the sample could not be rejected (Q = 12.05, df = 11, P = 0.36). The authors suggest that exercise may be a potential treatment to prevent or reduce depressive symptoms in individuals with MS, but existing studies do not allow solid conclusions. The authors also point out the need for future well-designed studies to evaluate the effects of exercise on depressive symptoms and major depression disorder in MS.[38]

A meta-analysis of randomized controlled trials (RCT) was carried out to explore exercise training and depression as an outcome in people with MS. The findings indicate that the weighted mean effect size was small, but statistically significant (Hedge's g = 0.36, SE = 0.09, 95% CI = 0.18–0.54, z = 3.92, p < .001) suggesting that exercise training somewhat improved depressive symptoms compared to control. Although the overall effect was not heterogeneous (Q = 16.46, df = 12, p = 0.17, I^2 = 27.08). A post-hoc, exploratory analyses only identified depression symptom scale as a potential moderator variable (not an outcome variable) (p = 0.04). This cumulative evidence indicates that exercise training can yield a small, but statistically significant and reliable reduction in depressive symptoms for people with MS.[39]

MANAGEMENT

RELAPSE

There is currently no literature or data on rates of relapse, but awareness of relapse is necessary when managing depression in patients with MS. This is because depression is different in MS than depression in the general population. Anecdotally, if these patients stop taking their antidepressant the relapse occurs almost immediately. Therefore general principles of relapse management should apply.

Consider long-term strategies such as prescribing long-term antidepressants and/or continuation or additional CBT sessions when there is a high risk of depression relapse, e.g., in circumstances of stress, comorbidity or for patients with a history of prolonged, severe or highly recurrent episodes of depression

FOLLOW-UP

Adequate follow up of patients with MS and depression is no different than follow up of any patient with depression and a chronic condition, and should be based on good clinical practice.

For patients with MS are likely involved with other secondary care providers, i.e., community neurology clinics, and some may be followed in tertiary care settings. Often there can be challenges when patients are managed by multiple care providers and there is no coordination of and/or clear communication among care providers in regards to who will manage the patient's depression. This may result in failure of the patient to succeed with treatment and/or become lost to follow up. When management is shared among multiple providers, i.e., primary and secondary care, there should be good communication and agreement between practitioners (especially the patient's primary care provider) in regards to who will be responsible for treating and monitoring the depression for that patient. The treatment plan should be shared with the patient and, where appropriate, with their family or caregiver.[40]

Collaborative care has also been suggested for patients with moderate to severe depression and a chronic health problem with associated functional impairment and having had no response to initial high-intensity medication, psychological interventions or some combination of interventions.[40] ICE Guideline 2009)

Collaborative care usually involves some form of case management supervised and supported by a mental health professional in close collaboration with primary and secondary physical health care providers. A multidisciplinary comprehensive care plan is constructed that includes: patient education, psychological and pharmacological interventions, medication management, and long-term coordination of care and follow-up. There is some evidence to support collaborative care in people with moderate to severe depression and a chronic physical health problem. However, the evidence regarding the effects of collaborative care on physical health outcomes is more limited. [40] However, improved depression care is thought to produce other health benefits, such as improved functioning and physical outcomes.[41]

Currently it is challenging to implement collaborative care in a community setting in Alberta because "case manager" positions do not exist in this setting for this purpose. However, collaborative care

with case management is provided within Alberta Health Services where some programs are organized with, and care is provided by multidisciplinary care teams.

IMPLEMENTATION CONSIDERATIONS

- Identify patients with MS in physician practice.
- Community neurologists identifying depression in their MS patients can provide/attach the TOP CPG with the consult notes to the primary care physician.
- Primary care physicians who have patients with MS might explore options for a notation or flag, regarding possible depression risk with a link to the CPG, within the patient's medical record.

REFERENCES

1. Siegert RJ, Abernethy DA. Depression in multiple sclerosis: A review. J Neurol Neurosurg Psychiatr. 2005 Apr;76(4):469-75.
2. Minden SL, Orav J, Reich P. Depression in multiple sclerosis. 1987. Gen Hosp Psychiatry. 1987 Nov;9(6):426-34.
3. Sadovnick AD, Remick RA, Allen J, Swartz E, Yee IML, Eisen K, Farquhar R, Hashimoto SA, Hooge J, Kastrukoff LF, Morrison W, Nelson J, Oger J, Pat, DW. 1996. Depression and multiple sclerosis. Neurology. 1996 Mar;46(3):628-32.
4. Patten SB, Beck CA, Williams JVA, Barbui C, Metz LM: Major depression in multiple sclerosis: a population-based perspective. Neurology. 2003 Dec 9;61(11):1524-7.
5. Marrie RA, Fisk JD, Yu BN, Leung S, Elliott L, Caetano P, et al. Mental comorbidity and multiple sclerosis: Validating administrative data to support population-based surveillance. BMC Neurol. 2013 Feb 6;13:16.
6. Patten SB, Newman S, Becker M, Riddell C, Metz L. Disease management for depression in an MS clinic. Int J Psychiatry Med. 2007;37(4):459-73.
7. Goldman Consensus Group. The Goldman Consensus statement on depression in multiple sclerosis. Mult Scler. 2005 Jun;11(3):328-37.
8. Patten SB, Berzins S, Metz LM. Challenges in screening for depression in multiple sclerosis. Mult Scler. 2010 Nov;16(11):1406-11.
9. Fragoso YD, Adoni T, Anacleto A, da Gama PD, Goncalves MVM, Matta AP da C, et al. Recommendations on diagnosis and treatment of depression in patients with multiple sclerosis. Pract Neurol. 2014 Aug;14(4):206-9.
10. Patten SB, Burton JM, Fiest KM, Wiebe S, Bulloch AG, Koch M, et al. Validity of four screening scales for major depression in MS. Mult Scler. 2015 Jul;21(8):1064-71. Doi: 10.1177/1352458514559297. Epub 2015 Jan 12.
11. Amtmann D, Kim J, Chung H, Bamer AM, Askew RL, Wu S, et al. Comparing CESD-10, PHQ-9, and PROMIS depression instruments in individuals with multiple sclerosis. Rehabil Psychol. 2014 May;59(2):220-9.
12. Pompili M, Forte A, Palermo M, Stefani H, Lamis DA, Serafini G, et al. Suicide risk in multiple sclerosis: a systematic review of current literature. J Psychosom Res. 2012 Dec;73(6):411-7.
13. Ramasubbu R, Taylor VH, Samaan Z, Sockalingham S, Li M, Patten S, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and select comorbid medical conditions. Ann Clin Psychiatry. 2012 Feb;24(1):91-109.
14. Patten SB. Antidepressant treatment for major depression in multiple sclerosis. International Journal of MS Care. 2009 Aug 1;11(4):174-9.
15. Koch MW, Glazenborg A, Uyttenboogaart M, Mostert J, De Keyser J. Pharmacologic treatment of depression in multiple sclerosis. Cochrane Database Syst Rev. 2011;(2):CD007295.
16. Henze T, Rieckmann P, Toyka KV, Multiple Sclerosis Therapy Consensus Group of the German Multiple Sclerosis Society. Symptomatic treatment of multiple sclerosis. Multiple Sclerosis Therapy Consensus Group (MSTCG) of the German Multiple Sclerosis Society. Eur Neurol. 2006;56(2):78-105.

17. Feinstein A, O'Connor P, Feinstein K. Multiple sclerosis, interferon beta-1b and depression A prospective investigation. J Neurol. 2002 Jul;249(7):815-20.

18. Borràs C, Río J, Porcel J, Barrios M, Tintoré M, Montalban X. Emotional state of patients with relapsing-remitting MS treated with interferon beta-1b. Neurology. 1999 May 12;52(8):1636-9.

19. Parfenov V, Schluep M, Du Pasquier R. Assessing risks of multiple sclerosis therapies. J Neurol Sci. 2013 Sep 15;332(1-2):59-65.

20. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue E-W, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):911-23.

21. Svenningsson A, Falk E, Celius EG, Fuchs S, Schreiber K, Berkö S, et al. Natalizumab treatment reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. PLoS ONE. 2013;8(3):e58643.

22. Cohen JA, Barkhof F, Comi G, Hartung H-P, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010 Feb 4;362(5):402-15.

23. Kappos L, Radue E-W, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis. N Eng J Med. 2010 Feb 4;362(5):387-401.

24. Laroni A, Brogi D, Morra VB, Guidi L, Pozzilli C, Comi G, et al. Safety of the first dose of fingolimod for multiple sclerosis: results of an open-label clinical trial. BMC Neurol. 2014 Apr 1;14:65.

25. Mohr DC, Likosky W, Bertagnolli A, Goodkin DE, Van Der Wende J, Dwyer P, et al. Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. J Consult Clin Psychol. 2000 Apr;68(2):356-361.

26. Beck AT. Cognitive therapy and the emotional disorders. Oxford: International Universities Press; 1976.

27. Arnett PA, Higginson CI, Voss WD, Randolph JJ, Grandey AA. Relationship between coping, cognitive dysfunction and depression in multiple sclerosis. Clin Neuropsychol. 2002 Aug;16(3):341-55.

28. Dennison L, Moss-Morris R, Chalder T. A review of psychological correlates of adjustment in patients with multiple sclerosis. Clin Psychol Rev. 2009 Mar;29(2):141-53.

29. Lynch SG, Kroencke DC, Denney DR:The relationship between disability and depression in multiple sclerosis: The role of uncertainty, coping, and hope. Mult Scler. 2001 Dec;7(6):411-6.

30. Mohr DC, Cox D. Multiple sclerosis: empirical literature for the clinical health psychologist. J Clin Psychol. 2001;57:479-99.

31. McCabe MP, McKern S, McDonald E. Coping and psychological adjustment among people with multiple sclerosis. J Psychosom Res. 2004 Mar;56(3):355-61.

32. Dennison L, Moss-Morris R. Cognitive-behavioral therapy: what benefits can it offer people with multiple sclerosis? Expert Rev Neurother. 2010 Sep 10;(9):1383-90.

33. Voss WD, Arnett PA, Higginson CI, Randolph JJ, Campos MD, Dyck DG. Contributing factors to depressed mood in multiple sclerosis. Arch Clin Neuropsych. 2002 Feb;17(2):103-15.

34. Hind D, O'Cathain A, Cooper CL, Parry GD, Isaac CL, Rose A, et al. The acceptability of computerised cognitive behavioural therapy for the treatment of depression in people with chronic physical disease: A qualitative study of people with multiple sclerosis. Psychol Health. 2010 Jul;25(6)699-712.

35. Spurgeon JA, Wright JH. Computer-assisted cognitive-behavioral therapy. Curr Psychiatry Rep. 2010 Dec;12(6):547-52.

36. Hind D, Cotter J, Thake A, Bradburn M, Cooper C, Isaac C, et al. Cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: a systematic review and meta-analysis. BMC Psychiatry. 2014;14:5.

37. Minden SL, Feinstein A, Kalb RC, Miller D, Mohr DC, Patten SB, et al. Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014 Jan 14;82(2):174-81.

38. Dalgas U, Stenager E, Sloth M, Stenager E. The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature. Eur J Neurol. 2015 Mar;22(3):443-e34.

39. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: Results of a meta-analysis. J Psychosom Res. 2014 Jun;76(6):465.

40. National Collaborating Centre for Mental Health. Depression in adults with chronic physical health problem: Recognition and management. Manchester, UK: NICE. 2009. Report No:CG91.

41. Katon W, Unutzer J, Fan M Y, et al. Cost-effectiveness and net benefit of enhanced treatment for depression for older adults with diabetes and depression. Diabetes Care. 2006 Feb;29(2):265-70.

SUGGESTED CITATION

Toward Optimized Practice (TOP) MS in Depression Working Group. 2015 December. Identification and management of depression in multiple sclerosis: Clinical practice guideline. Edmonton, AB: Toward Optimized Practice. Available from: http://www.topalbertadoctors.org

For more information see www.topalbertadoctors.org

GUIDELINE COMMITTEE

The committee consisted of representatives of family medicine, psychiatry, neurology and psychology.

December 2015

APPENDIX A – DEPRESSION ASSESSMENT TOOLS

Screening Tool	Advantages	Disadvantages
PHQ-9 http://www.med.umich.edu/1info/FHP/practiceguides/depress/phq-9.pdf	In public domain and commonly used Well known and high quality Relatively quick and easy to use No copyright fees/no permission required to use Aligns with DSM-5 diagnostic concepts	
CES-D (20 item) symptom scale http://www.depression-help-resource.com/cesd-depression-test.pdf	In the public domain and commonly used No copyright fees/no permission to use	Longer than PHQ-9 (20 items) Doesn't align as closely with the DSM-5 diagnostic concepts
Beck (BDII) http://www.pearsonclinical.com/psychology/products/100000776/beck-family-of-assessments.html#tab-details	Second iteration of the Beck depression inventory More aligned with DSM than the previous version. Focuses on cognitive symptoms (altered thinking style) rather than somatic symptoms of depression. Avoids "confounding" of MS symptoms with depression ratings	Under copyright and permission/fee to use
HADS (Hospital Anxiety & Depression Scale) http://opencourses.emu.edu.tr/pluginfile.php/8619/mod_resource/content/1/HADS.pdf	Depression and anxiety rating (each seven items) Designed for medically ill population and avoids somatic symptoms	Under copyright and permission/fee to use Created in the UK so language used is poorly understood in North America
Beck Depression Inventory (BDI) "fast screen" A subset of BDI items http://www.pearsonclinical.com/psychology/products/100000776/beck-family-of-assessments.html#tab-details	Recommended by Benedict et al. for assessment of MS patients.	Under copyright and permission/fee to use
Zung Self-rating depression scale http://healthnet.umassmed.edu/mhealth/ZungSelfRatedDepressionScale.pdf	In the public domain No copyright fee/no permission to use	Not as popular lately
The Quick Inventory of Depressive Symptoms (QIDS) http://www.ids-qids.org/tr-english.html	Scale that is becoming popular especially for use in research. No copyright fee/no permission to use	Long

APPENDIX B – MEDICATION TABLES

Class of Medication	Medication
Tricyclics	amitriptyline (Elavil®) nortriptyline (Aventyl®, Pamelor®)
Selective Serotonin Reuptake Inhibitors (SSRIs)	citalopram (Celexa®) fluoxetine (Prozac®) paroxetine (Paxil®) sertraline (Zoloft®)
Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)	mirtazapine (Remeron®) venlaflxine (Effexor®) desvenlaflaxine (Pristiq®)

Table 1: Common Antidepressants Used for Depression in Patients with MS

Source: MS Society of Canada

Common Drugs for Treating MS	MS Drug – Antidepressant Interaction *Note: X = no known interaction*
Aubiagio® (teriflunomide)	X
Avonex® (interferon beta 1a) Betaseron (interferon beta 1b) Copaxone® (glatiramer acetate) Extavia® (interferon beta 1b) Rebif® (interferon beta-1a)	• Increased risk of depression • Monitor patients with a history of depression – depression symptoms can worsen.
Gilenya® (fingolimod)	• Possible bradycardia risk when initiating antidepressant • Pts with prolonged QTc can have arrhythmia. • The combination can be used as long as the ECG is monitored in the first month and after dose increases. Use clinical judgement (based on the ECG result) to determine monitoring frequency. • Do not prescribe QTc-prolonging drugs to anyone with a QT>440 ms (female) or 420 ms; male); do not allow the QTc interval to exceed 500 ms during titration with these drugs. • Be aware of and avoid interactions that result in increased exposure to either agent.
Lemtrada™ (alemtuzumab)	X
Tecfidera™ (dimethyl fumarate)	X
Tysabri® (natalizumab)	X

Table 2: MS Drugs and Antidepressant Interactions

APPENDIX C – NON-PHARMACOTHERAPY

Approach	Description	Contact information
Cognitive behavioural therapy (CBT)	Many primary care networks (PCNs) offer doctoral level psychologists and/or behavioural health consultants that can provide CBT: • Individual • Group • Telephone	Consult your PCN regarding CBT. Employed patients should contact their employee assistance programs (EAP). See Appendix D for mental health services available in AB that may provide CBT and/or other therapies.
CBT Self-help – web based **MoodGYM**	MoodGYM Training Program is a free, interactive program consisting of five modules, which helps individuals explore: • Why they feel the way they do • Changing the way they think • Knowing what makes them upset • Assertiveness and interpersonal skills training	https://moodgym.anu.edu.au/welcome/new/splash
Self-help manuals/books • The Antidepressant Skills Workbook (ASW) © 2009 Centre for Applied Research in Mental Health and Addiction (CARMHA) and BC Mental Health & Addiction Services (BCMHAS)	Provides an overview of depression, explains how it can be effectively managed according to the best available research, and gives a step-by-step guide to changing patterns that trigger depression. The self-care guide explains how to use **cognitive and behavioural methods** and can be used in combination with other depression treatments. *Note: use of this self-help guide alone is not sufficient to resolve serious/major depression.*	ASW and self-care guide and audio book are available in the public domain. Hard copies can be purchased see website link for more details: http://www.comh.ca/antidepressant-skills/adult/index.cfm
• Mind Over Mood: Change how you feel by changing the way you think. Authors: Dennis Greenberger and Christine Padesky	Step-by-step worksheets teach specific skills to address depression, panic attacks, anxiety, anger, guilt, shame, low self-esteem, eating disorders, substance abuse and relationship problems. Mood questionnaires are included to identify, rate, and track changes in feelings; change the thoughts that contribute to problems; follow step-by-step strategies to improve moods; and take action to improve daily living and relationships.	Available for purchase online at: http://www.amazon.ca/Mind-Over-Mood-First-Edition/dp/0898621283
• The Stress and Mood Management Program for Individuals with Multiple Sclerosis. Author: David Mohr	MS-specific and based on the principles of cognitive behavioural therapy (**CBT**) (paperback workbook)	Available for purchase online at: http://www.amazon.ca/Management-Program-Individuals-Multiple-Sclerosis/dp/0195368894

APPENDIX D – MENTAL HEALTH SERVICES

Service Area	Contact	Description
Province-wide		
Crisis Services Alberta Mental Health Help Line	Alberta-Wide Web and / or Telephone Access 1-877-303-2642	Staffed 24/7 by health professionals, the Mental Health Help Line provides crisis intervention, information on mental health programs and services, and referral to other agencies where appropriate. This confidential, anonymous service is provided by Health Link Alberta and is available to all Albertans.
Alberta Health Services Edmonton and Area or phone 811 for Health Link		
General Counselling Services Community Mental Health Clinics – Edmonton and Area	https://informalberta.ca/public/service/serviceProfileStyled.do?serviceQueryId=7575	Crisis intervention including: • Urgent services assessment for individuals experiencing significant functional problems related to mental health issues • Short-term and longer term treatment for people with severe or persistent mental disorders or moderate to severe emotional distress which could include issues such as depression, schizophrenia, anxiety, suicide and anger management, etc. Available to children (five and over) and adults with a severe or persistent mental disorder or moderate to severe emotional distress. Telephone inquiries are welcome. Self-referrals are accepted. Referrals are also received from family physicians, pediatricians, other health service providers (the person being referred must give consent).
Crisis Services in Edmonton		
The Support Network-Crisis Support Line	24 hours:1-800-232-7288 (Toll free service available to northern Alberta) 24 hours: (780) 482-HELP (4357) http://www.crisissupportcentre.com	
Walk-in Counselling Society of Edmonton (WISCOE)	GB Building, 200- 9562 82 Ave Edmonton T6E 0Z8 780-757-0900 Tuesday-Thursday 1-7pm Friday-Saturday 10 am – 2 pm Sunday-Monday closed	Offers a single session approach to counselling for individuals, couples and families on a first-come, first-serve basis. Services are free or on a sliding scale. Sometimes clients are referred to other services.
Salvation Army Community & Family Centres – Hope Line	Hope Line: 780-424-9223 Monday-Friday 9 am – 11:30 pm http://vvww.salvationarmy.ca/alberta/	

Service Area	Contact	Description
Counselling Services in the Community-Edmonton		
Jewish Family Services	780-454-1194	
Catholic Social Services	780-432-1137	Sliding scale fees
Community Counselling Centre	780-482-3711	Sliding scale fees
YWCA	780-423-9922 ext. 222	
Cornerstone Counselling	780-482-3711	Sliding scale fees; student psychologist $20
The Family Centre	780-424-6103	
Insight Psychological Inc.	780-461-1717 (south) 780-478-2580 (north)	
Loussa Counselling Centre	780-478-4215	
North Land Family Counselling Group	780-439-5683	
Calgary and area or phone 811 for Health Link		
Access Mental Health	http://www.albertahealthservices.ca/11443.asp Service locations – see links below for more details about this service at various locations. http://www.albertahealthservices.ca/info/facility.aspx?id=1002752&service=2381 403-943-1500 Ext 1 (Child/Adolescent Services) 403-943-1500 Ext 2 (Adult and Senior Services)	AHS and other mental health resources are found on the AHS Access Mental Health website.