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Review article

Treating depression in multiple sclerosis with antidepressants: A brief review of clinical trials and exploration of clinical symptoms to guide treatment decisions

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ABSTRACT

Depression is a common comorbidity in patients with multiple sclerosis (MS). Those with MS and concurrent depression have poorer quality of life and are also less likely to be compliant with disease-modifying treatment, which may ultimately affect their MS disease course. Treating depression in MS with pharmacological agents can improve not only depression, but may also impact the MS disease course. However, no guidelines exist around treating depression in MS. Few randomized-controlled trials using antidepressants in MS exist. Here, we briefly review trials using antidepressant medications to treat depression in MS. We also propose individualizing treatment of depression in MS, as the depressive symptoms and MS symptoms and disease course differ significantly between patients. We explore the heterogeneity in presentation of depression through different comorbid symptoms in MS, and discuss which antidepressant options would be appropriate in each situation. We propose that future clinical trials should incorporate differences in issues between those with depression (e.g. sexual dysfunction, urinary incontinence) into analysis. As MS is incredibly heterogeneous, treating concurrent depression on a case-by-case basis may enable for improving quality of life and the MS disease course.

1. Introduction

Depression is a common comorbidity of multiple sclerosis (MS), with numerous studies reporting that approximately 25% of those with MS also have depression (Patten et al., 2003; Marrie et al., 2015). The risk of developing depression in MS over one's lifetime is as high as 50% (Minden and Schiffer, 1990). Depression has a negative effect on patients' quality of life, and in particular, is second only to disability status in affecting health-related quality of life in MS (Berrigan et al., 2016). Depression can also factor into decreased adherence to disease-modifying therapies in MS (Treadaway et al., 2009; Tarrants et al., 2011). The causes of depression in MS are currently not well understood, but are presumed to be multifactorial in nature.

Historically, depression was undertreated in MS (Mohr et al., 2006; Cetin et al., 2007). However, a survey-based study recently done in Calgary, Canada found that 85.7% of their MS patients with depression are receiving treatment for depression (Raissi et al., 2015). Although a high percentage of patients were being treated, depressive symptoms still persisted, which were hypothesized to be possibly due to an inadequate dose and an ineffective antidepressant agent (Raissi et al., 2015). Treating depression in MS with antidepressants has been shown to be effective (Patten, 2009), although studies in this area are lacking. Aside from treating depression itself, the antidepressant escitalopram has been shown to significantly reduce stress-related relapses in women in a randomized-control trial (Mitsonis et al., 2010). This suggests that the use of antidepressants in MS is not limited only to treating depression, but may also impact the MS disease course. Another antidepressant, vortioxetine has appeared promising not only for treating depression, but also for improving cognition (Frampton, 2016), a significant outcome considering that cognitive impairment is present in approximately half of MS patients (DeSousa et al., 2002). Although some trials have shown positive benefits in cognition with vortioxetine (McIntyre et al., 2014; Mahableshwarkar et al., 2015), an FDA report from 2016 has not endorsed any antidepressant for its effects on cognition, including vortioxetine (FDA, 2016). A recent Cochrane review on the use of vortioxetine in depression did not include cognition as a reported outcome either (Koesters et al., 2017). Furthermore, no trials have used vortioxetine in MS patients to treat depression as of yet.

Another possible option for treating depression in MS is the use of cognitive behavioral therapy. A recent systematic review and meta-analysis reported that depression severity in MS improved with psychological therapy, including cognitive behavioral therapy (Fiest et al.,

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2016). Although cognitive behavioral therapy has been shown to be effective for depression in MS (Mohr et al., 2001; Cosio et al., 2011; Moss-Morris et al., 2013; Graziano et al., 2014), it is outside the scope of this article and will not be discussed further here.

One of the main issues present when treating depression in MS is the fact that some of the side effects of anti-depressants can worsen deficits related to the MS disease course. For example, selective serotonin reuptake inhibitors (SSRIs) may cause or exacerbate sexual dysfunction, which may already be problematic for many patients. One study cited the percent of women with MS with sexual dysfunction as ranging from 34% to 85% (Cordeau and Courtois, 2014) while another study found that over 50% of men with MS report erectile dysfunction and over 25% report decreased sexual desire (Lew-Starowicz and Rola, 2014).

Furthermore, the MS disease course is sufficiently heterogeneous that a single SSRI which is beneficial for one patient with a certain MS disease profile may not be a good option for a different MS patient, even if both fall under the same subtype of MS (ie. relapsing-remitting, secondary-progressive, primary progressive, progressive-relapsing). Given the lack of evidence-based management guidelines for the treatment of depression in MS, the choice of treatment is frequently determined by physician preference and experience. An approach to medication selection for depression in MS has been previously included in a larger review of symptomatic therapies in MS (Jarvis et al., 2013). In this paper, we briefly review trials using antidepressants in MS and propose using clinical decision making to select antidepressants in MS, taking into account each patient's MS disease course as well as comorbidities or other issues concurrent with their depression.

2. Pharmacotherapy for depression in MS

To date, only three randomized-controlled trials have been carried out for antidepressant treatment for MS. The agents trialed were paroxetine (Ehde et al., 2008), sertraline (Mohr et al., 2001), and desipramine (Schiffer and Wineman, 1990). There have also been four open-label trials with duloxetine (Solaro et al., 2013), fluvoxamine (Benedetti et al., 2004), moclobemide (Barak et al., 1999), and sertraline (Scott et al., 1995). These trials have been reviewed extensively by others (Koch et al., 2011; Fiest et al., 2016), so they will only be discussed briefly here.

Among the antidepressants tested in randomized-controlled trials against placebo, sertraline was effective at reducing depression in a trial involving 63 MS patients as measured with the Beck Depression Inventory (BDI), but not the Hamilton Depression Rating Scale (Mohr et al., 2001). On the contrary, desipramine was effective at reducing depression as measured with the Hamilton Rating Scale, but not the Beck Depression Inventory in a trial where 14 MS patients received placebo and psychotherapy while another 14 MS patients received desipramine and psychotherapy (Schiffer and Wineman, 1990). Paroxetine did not provide a statistically significant improvement in depression compared to placebo as measured using the Hamilton Rating Scale in a trial involving 42 MS patients (Ehde et al., 2008).

The American Academy of Neurology published a consensus statement in 2014 that concluded that there is not enough evidence to support or refute the efficacy of paroxetine, sertraline, and desipramine based on the randomized-controlled clinical trials described above (Minden et al., 2014). The consensus statement cites a variety of issues in each of the studies including non-randomization and studies being underpowered, and ultimately states that there is a lack of evidence for these antidepressants in patients with MS (Minden et al., 2014). On the contrary, a Cochrane review from 2011 on pharmacological agents for treating depression in MS concluded that there is likely efficacy for paroxetine and desipramine for treating depression in MS, but that these medications have significant side effects and the studies ultimately lost many patients to follow-up with missing outcome measures (Koch et al., 2011). The study using sertraline was not included in the Cochrane review.

Between the randomized-controlled trials described above and the reviews on these studies to date, it is clear that there is still some debate as to the benefits of antidepressants to treat depression in MS, particularly with the adverse effects encountered with some of these medications. However, there are positive benefits of antidepressants on some individuals with MS; this warrants further exploration in the form of more rigorous randomized-controlled trials.

Antidepressants used in open-label trials have showed some effectiveness in reducing depression. Duloxetine was used in an open label study for either four weeks or 12 weeks at a dose of 60 mg daily in 75 MS patients where it was found to significantly reduce scores in the BDI and Modified Fatigue Impact Scale for both durations of treatment (Solaro et al., 2013). Fluovaxmine was trialed for three months at a maximum dose of 200 mg daily in 43 MS patients who were taking interferon-β as a disease modifying therapy, where it significantly improved scores on the Montgomery-Asberg Depression Rating Scale, regardless of baseline neuropsychological status (Benedetti et al., 2004). A three month small scale open label trial with 10 MS patients using moclobemide (at doses ranging from 150 to 400 mg) showed complete remission in nine MS patients (Barak et al., 1999). Another small scale study in open label format used sertraline (100 mg daily) in 11 MS patients which also demonstrated effectiveness as measured by the Carroll Scale after three months of treatment (Scott et al., 1995).

It is worth noting that all of the above trials have each used fewer than 100 MS patients in their studies, making it very difficult to generalize what the effects of such medications would be on one with depression in the context of MS. Furthermore, many of the agents listed above are not well-tolerated in comparison to other available antidepressants.

Taking into account the fact that there are no guidelines currently in place for treating depression in MS, and that MS is an immensely heterogeneous disease, we will seek to discuss the process one could use to select an antidepressant in certain situations.

2.1. Nausea and insomnia

In MS patients suffering with nausea or insomnia concurrent with their depression, with or without cachexia, the clinician ought to consider antidepressant treatment with mirtazapine. Mirtazapine blocks inhibitory presynaptic α_2-adrenergic autoreceptors and also blocks 5-HT_2 and 5-HT_3 receptors, thereby increasing norepinephrine and serotonin transmission, respectively (Anttila and Leinonen, 2001). Insomnia, which is common among those with depression, can be alleviated with mirtazapine (Winokur et al., 2003). Compared with other antidepressants, mirtazapine is less likely to cause nausea (Watanabe et al., 2011), and in fact, can be an effective treatment for nausea (Pae, 2006). Mirtazapine has been useful for nausea and insomnia in cancer patients (Kim et al., 2008). Mirtazapine can also induce weight gain (Masand and Gupta, 2002; Serretti and Mandelli, 2010; Domecq et al., 2015) which could be beneficial for a patient who has difficulty keeping weight on.

2.2. Sexual dysfunction

Mirtazapine may be considered for patients suffering from sexual dysfunction as it is less likely to cause adverse sexual side effects compared to SSRIs (Benkert et al., 2000; Baldwin, 2001), and may instead help improve sexual function in those with sexual dysfunction concurrent with depression (Saiz-Ruiz et al., 2005). Currently, studies looking at the use of mirtazapine to treat depression in the context of MS are lacking.

Bupropion (Wellbutrin) should also be considered in a patient with sexual dysfunction. Bupropion is a norepinephrine-dopamine reuptake inhibitor (NDRI) that does not have significant serotonergic effects (Stahl et al., 2004) unlike most antidepressants, and is associated with a low risk of sexual dysfunction when compared head-to-head with other

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