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Review Article

A Review of Mirtazapine Use for Primary Providers

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Abstract

1. Although clinical trials have demonstrated the effectiveness of mirtazapine in treating major depressive disorder more studies are needed to confirm its efficacy in treating generalized anxiety, insomnia, behavior disorders, substance use disorders, movement disorders, pain, weight loss, postoperative nausea and vomiting., and other medical conditions.
2. Primary care providers prescribing mirtazapine may need to acquire knowledge about its the basic pharmacology, adverse effects, and dosing guidelines.
3. Based on its rapid onset of action, its relatively favorable side-effect profile and its safety in overdose attempts, mirtazapine seems to offers many advantages for primary care providers in regard to its therapeutic use in the treatment of various psychiatric and medical conditions.

Keywords: *Mirtazapine; Primary Care; Pharmacology; Psychiatric; Medical; Neurological*

Introduction

Since its introduction in the United States in 1996, the use of the antidepressant mirtazapine in a wide range of conditions has been growing. According to the Report of the Surgeon General Working Meeting on the Integration of Mental Health Services and Primary Care Health Care [1], a great majority of patients with mental health issues usually seek out primary care providers rather than psychiatrists and mental health professionals for fear of social stigmatization. Family practice physicians, internists, physician assistants, nurse practitioners, and clinical nurse specialists are usually the primary care providers that evaluate and initiate pharmacological treatment for many patients with psychiatric disorders. This article reviews the history, basic pharmacology, adverse effects, dosing guidelines, and the various off-label indications for mirtazapine. It is hoped that the review would familiarize primary care providers with the broad spectrum beneficial effects of the antidepressant mirtazapine.

History

Mirtazapine is an antidepressant which was first used in The Netherlands in 1987 and approved in the United States in 1996 [2]. As an antidepressant, mirtazapine is not chemically related to any other class of antidepressants. It belongs to a unique tetracyclic compound known as piperazinoazepines and is associated with fewer adverse effects than the tricyclic antidepressants (TCAs) and as such, it is better tolerated [3,4]. Compared to the TCAs and some serotonin reuptake inhibitors (SSRIs,) mirtazapine may have a faster onset of antidepressant efficacy, with maximal effects within 2 to 4 weeks of adequate dosage selection. Mirtazapine's initial FDA approval was granted in

June 1996 for treatment of depression in adults, and in 2002, another approval was granted for its use in maintaining a response in adults with major depressive disorder [5,6]. It is important for clinicians to know that since 2004, all antidepressants including mirtazapine have, a Black Box warning, of increased risk of suicidality in children, adolescents, and young adults.

Basic Pharmacology

Mirtazapine (Remeron®) has both noradrenergic and serotonergic properties. Its primary mechanism of action is blockade of the presynaptic α2-adrenergic receptor in addition to blocking the 5-HT2 and 5-HT3 receptors. Antagonism at presynaptic α2-adrenergic receptors (autoreceptors) increases norepinephrine (NE) release. Increased NE facilitates 5-HT release via α1-adrenergic receptors on 5-HT neurons. This action is augmented by mirtazapine's α2-adrenergic antagonism at the presynaptic α2-adrenoreceptor on 5-HT neurons (Heteroreceptors) and resultant disinhibition of 5-HT release. Mirtazapine's potent antagonism at the 5-HT2 and5-HT3 receptors underlies its anxiolytic and hypnotic properties, as well as its low incidence of activating (5-HT2) and gastrointestinal (5-HT3) side effects [7] in addition to its generally milder side effects profile [8].

Mirtazapine is well absorbed by the gastrointestinal tract, and its bioavailability does not appear to be affected by the presence of food and is extensively metabolized in the liver, and 75% of its metabolites are primarily eliminated in the urine and in the feces [9]. Its pharmacokinetics could be affected by gender, age, and organ dysfunctions especially in the presence of hepatic and renal impairments. It has a half-life of 20 – 40 hours, which may increase by 30% – 40% in patients with hepatic impairment [9], and its clearance may decrease by 30% – 50% in patients with moderate-to-severe renal impairment. The oral clearance of mirtazapine is reduced in elderly patients with elderly males exhibiting a 40% lower clearance, while elderly females had a 10% lower clearance when compared to younger adults. Females of all ages exhibit significantly longer elimination half-lives of mirtazapine compared to males. Mirtazapine does not auto-induce hepatic isoenzymes and has a low potential for drug–drug interactions [10].

Adverse Effects

The most commonly reported adverse effects are transient somnolence, increased appetite and weight gain, which may be attributed in part to mirtazapine's antihistaminic activity [11]. Although no specific laboratory monitoring is recommended with mirtazapine treatment, there have been reports of elevations in liver enzymes lipids, and agranulocytosis [12]. These side effects are generally reversible with the discontinuation of mirtazapine. Thus clinicians need to monitor for the development of symptoms like fever, sore throat, stomatitis or other signs of infection; when these symptoms occur, mirtazapine treatment should be discontinued and complete blood count (CBC) monitoring should be initiated [13]. The co-administration of mirtazapine with other medications that potentiate the actions of serotonin such as the serotonin reuptake inhibitors (SSRIs), could theoretically result in serotonin syndrome [14]. Concurrent use of antipsychotics or other dopamine antagonists with serotonergic antidepressants may increase the potential for neuroleptic malignant syndrome (NMS) which is a potentially life-threatening complication that may include symptoms such as hyperthermia, muscle rigidity, autonomic instability, and mental status changes [15]. If serotonin syndrome or an NMS-like reaction becomes evident during treatment, mirtazapine and any nonessential serotonergic or antidopaminergic agents should be discontinued and appropriate medical treatment should be initiated.

Mirtazapine is not recommended for use in combination with mono amine oxidase inhibitors (MAOIs) therapy or within 14 days of initiating or discontinuing therapy with a MAOI and the concomitant use of MAOIs with other antidepressants have resulted in hypertensive crisis. So MAOIs should be discontinued 2 - 4 weeks before initiation of mirtazapine therapy [16].

Because the possibility of a suicide attempt is inherent in patients with depressive symptoms, patients with a history of suicidal ideation or behaviors and those with a prominence of suicidal ideation prior to treatment are considered at an increased risk for suicidal ideation or attempts, and should be closely monitored during treatment with mirtazapine. In adolescents and young adults, patients who exhibit changes in symptoms such as worsening of depression or emergent suicidality, a decision should be made to change or discontinue treatment [17]. If discontinuing, medication should be tapered as rapidly as possible, but with recognition that abrupt discontinu-

ation can also cause adverse symptoms. All antidepressants should be prescribed in the smallest quantity consistent with good patient management in order to reduce the risk of overdose [18].

Dosing Guidelines

Mirtazapine is available in an oral tablet form and as an oral rapidly disintegrating tablet [19]. The recommended daily dose for mirtazapine in adults is initially 15 mg orally at bedtime. The effective dose range is 15 - 45 mg/day. Dosage adjustments should not be made more often than every 1 - 2 weeks. Treatment with an adequate dose should result in a positive response within 2 - 4 weeks. If treatment discontinuation is necessary, a gradual dose reduction over several weeks is recommended. Abrupt discontinuation should be avoided if possible to prevent emergence of unpleasant side effects [20]. In geriatric patients, slower titration may be indicated, based on patients' response and tolerance. Initially, 7.5 mg orally at bedtime with dosage adjustments no more frequently than every 1 - 2 weeks, due to mirtazapine's long half-life and its reduced clearance in the elderly [21]. The safety and effectiveness of mirtazapine use has not been established in children and adolescents.

Mirtazapine Use in Psychiatric Conditions

Depressive Disorders

In the United States, depression is reported to be one of the most common psychiatric condition that present in a primary care setting [22]. Mirtazapine is approved for the treatment of mild to severe depression, it has also been uses to treat other types of depression as well as in the treatment of depression that is co-occurring with various medical conditions.

Recurrent Depression

Patients with recurrent depression who are treated with mirtazapine, could experience marked reductions in the severity, duration and frequency of their depressive episodes [23].

(Dysthymia)

Patients with dysthymic disorder could significantly improve with mirtazapine as long as they are able to tolerate its sedative effects which need to be differentiated from the vegetative symptoms of fatigue, tiredness, lack of energy and increased sleep that are associated with depression [24].

As an Augmenting agent for treatment resistant depression

Treatment resistant depression is generally frequently defined as depression that does not respond to two satisfactory trials of an antidepressant [25]. Treatment resistant depression is common, and the majority of patients treated with an initial trial of an antidepressant will not achieve remission [26,27]. Three main strategies are commonly used in patients with treatment resistant depression; 1) switch to another anti-depressant, 2) combine two anti-depressants with different mechanisms of action or 3) augment with a non-anti-depressant medication. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial was a landmark study that systematically assessed treatment options in the management of treatment resistant depression and found that combining anti-depressants, augmentation with a non-anti-depressant and switching are comparable in efficacy [26,27]. In some cases, switching may be beneficial over augmentation, as adherence is greater with simpler medication regimens [28] and may be greater with monotherapy [29]. However, it is important for clinicians to be aware of the role of personal factors in achieving a treatment response. In certain individuals who have had partial response to an antidepressant, monotherapy, adding a second antidepressant or augmentation with other agents may be preferable, whereas in individuals who have had no response or are having side effects, switching may be preferable. Mirtazapine's unique side effect profile makes it especially useful in patients with poor sleep and appetite given its effects of sedation and appetite stimulation, as well as its low propensity for gastrointestinal side effects [30]. Although the STAR*D trial did not find significant differences in regard to side effects between individuals who chose augmentation versus switching antidepressants [31]. In general, mirtazapine has been found to be effective in treatment resistance depression both as monotherapy [32] and as an augmenting agent to the SSRIs [33,34]. Augmenta-

tion with mirtazapine may even partially attenuate the sexual dysfunction, insomnia and gastrointestinal side effects of SSRIs due to its 5-HT2, 5-HT3 and histamine receptor blockade.

Depression in Geriatric Patients

Since depression is common in the elderly, primary care providers need to be able to identify it rather than attribute it to being old, or as being secondary to other medical concomitant conditions [22]. Elderly patients receiving mirtazapine for treatment of depression are less likely to need other anxiolytic or hypnotic agents, since mirtazapine could also lower their anxiety, improve their sleep, and as result, the incidence of multiple drug interaction would be minimized with the additional benefits of lowering overall medication costs [35].

Depression during menopause

Menopausal women who are deemed refractory to estrogen replacement treatment and who were depressed, could benefit from mirtazapine antidepressant actions [36,37]. Although some of these patients developed side effects of initial hot flashes and associated perspiration, these effects disappeared within a week, despite continued mirtazapine treatment [36].

Dementia with co-occurring depression

In general, the use of antidepressants to treat depression in patients with dementia is not recommended as first line treatment, with the exception in some patients with three months of ongoing depression despite the use of non- pharmacological and psychosocial interventions [38]. Mirtazapine has been used to treat patients with dementia of the Alzheimer's type, and was found to be beneficial in decreasing depressed mood, along with decreasing agitation and improving appetite without significant side effects or further cognitive deterioration [39].

Depression associated with myocardial infarction

The use of antidepressants including mirtazapine can be effective in treating post-myocardial depression which if left untreated could lead to increased cardiac morbidity and mortality [40]. Mirtazapine can also contribute to a decrease in post–myocardial infarction inflammatory markers [41].

Post- cerebrovascular accident (post-stroke) depression

Prophylactic treatment with mirtazapine on the first day following stroke was found to significantly reduce the rate of developing post-stroke depression, and it was also effective in treating post-stroke depression in patients who developed depression who did not receive it prophylactically [42]. In addition to its beneficial effects on post-stroke depression, mirtazapine was well tolerated when used in other cardio vascular conditions [43].

Depression due to human immunodeficiency virus

Since MDD has a higher prevalence in both human immunodeficiency virus (HIV)-positive group and at-risk group, mirtazapine has shown effectiveness in treating recurrent MDD in patients with HIV with a lower incidence of total adverse effects, with the exception of patients who would discontinue mirtazapine treatment because of side-effects and medical complications related to the HIV infection [44].

Transplant patients with anxiety and depression

The multiple psychological stressors, various medication effects and the physiological disturbances resulting from organ transplants are usually associated with depressive and anxiety disorders which if left untreated could lead to reduced functioning and quality of life [45]. Because of mirtazapine absence of sexual side-effects and gastrointestinal complaints and its low potential for drug interaction, particularly with immunosuppressive mirtazapine's agents, it can offer an advantage for use in transplant recipients. In addition, its sedative and weight gain effects could be beneficial in counteracting the decreased appetite or sleep disturbances in patients undergoing trans-

plantation [46]. However, clinicians need to avoid mirtazapine as first-line agents in these patients due to the potential exacerbation of immunosuppressant-induced metabolic changes resulting from corticosteroid-induced weight gain and hyperlipidemia [47].

Refractory anorexia nervosa and depression

According to case reports, mirtazapine may be useful for older, chronically ill patients with anorexia nervosa and co-occurring depression who have not responded to other treatment modalities. Patients treated with mirtazapine have been shown to usually gain weight and experience improvement in depression and general quality of life [48]. Controlled trials are needed in this direction [49].

Sleep disorders

In addition to mirtazapine effects on improving sleep patterns in depressed patients [50], it has also been shown to improve the percentage of time in bed spent sleeping, decrease nighttime awakenings and increase total time spent asleep [51,52]. This effect on sleep has also been observed in patients who suffer from insomnia even in the absence of depression. Although primary care clinicians usually consider insomnia and other sleep disorders as symptoms of other primary psychiatric conditions, sleep difficulties increase the risk for, and even directly contribute to, the development of psychiatric disorders. The treatment of sleep disorders may also help alleviate symptoms of co-occurring psychiatric disorders [53]. As such mirtazapine offers a safer alternative to the use of sedative hypnotics or benzodiazepines for the treatment of sleep difficulties, the latter having a potential for the development of addiction and lethal outcomes in overdose attempts.

Anxiety Disorders

Anxiety disorders are prevalent in primary care settings and mirtazapine can be used in the treatment of depression and co-occurring anxiety, as well as for the treatment of various anxiety disorders in patients who did not respond to the SSRIs, or the serotonin norepinephrine reuptake inhibitors (SNRIs), benzodiazepines or buspirone. The anxiety disorders that could benefit from mirtazapine treatment include generalized anxiety disorder [54], panic disorder [55] and social anxiety disorder (social phobia) [56].

Obsessive compulsive disorder

Because obsessive compulsive disorder (OCD) among adults in the United States has an estimated 12-month prevalence of 1.2 percent and an estimated lifetime prevalence of 2.3 percent, it is likely to present to primary care providers in the context of other co-occurring psychiatric and medical conditions [57]. Rather than being an anxiety disorder, it has been reclassified according to the diagnostic and statistical manual of mental disorders 5th edition (DSM-5) under the category Obsessive-Compulsive and Related Disorders [5]. The SSRIs are usually the first treatment of choice for OCD. Switching between various SSRIs is usually recommended by various treatment guidelines, and approximately 50% of patients with OCD who do not respond to one SSRI will respond to another one, however, the response rate may decrease as a third or fourth SSRI is tried [58]. Some patients may respond to the augmentation of an SSRI with another non-SSRI antidepressant, such as mirtazapine [59]. When mirtazapine is added to an SSRI, an earlier onset of response in OCD symptoms and reduced undesired side-effects are usually observed by clinicians and reported by patients. Some patients with treatment resistant OCD have also responded to treatment with mirtazapine alone [60].

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a chronic condition, with a high lifetime prevalence rate of 7.8%, which is usually associated with increased rates of other co-occurring psychiatric and medical conditions [61]. PTSD has been reclassified according to DSM-5 under the category of Trauma and Stressor-Related Disorders [5]. Mirtazapine could contribute to a general reduction of PTSD symptoms especially those that are related to the associated sleep disturbances [62]. In addition, mirtazapine's sedative effects may help lessen the hyperarousal which prevents patients with PTSD from falling asleep, and can also lead to increasing the stages of slow-wave, restorative sleep [30].

Schizophrenia

The negative features of schizophrenia which, include blunted affect, poverty of thought content and speech, avolition or apathy and social withdrawal although they differ from depression, may respond to antidepressant treatment [63]. Mirtazapine has shown a potential as an augmenting agent for the treatment of negative symptoms of schizophrenia [64].

Capgras syndrome

Capgras syndrome, is a delusional psychiatric condition characterized by mis-identification, where patients believe that their relatives or significant other have been replaced by impostors. Mirtazapine was found to be beneficial in treating a case of Capgras syndrome [65].

Substance use disorders

Insomnia and depression are frequently encountered in patients during withdrawal from substance use. While there are no approved medications for treating them, mirtazapine has shown some promising results in the treatment of substance-induced sleep and mood disorders, and can be used across a number of substance use disorders (SUDs)as summarized in the following section [66].

Alcohol use and co-occurring depression

Patients with alcohol use disorder and co-occurring depressive disorder, demonstrated significant improvement in their degree of depressive symptoms and alcohol craving scores with antidepressants including mirtazapine and amitriptyline, and most patients tolerated mirtazapine better than amitriptyline [67].

Management of alcohol withdrawal

Mirtazapine can improve the effects of cognitive-behavioral therapy on stabilizing social anxiety symptoms in patients with alcohol use disorder who completed alcohol withdrawal treatment, and could also decrease the duration of anxiety and depressive symptoms when administered in combination with psychotherapy during the post alcohol withdrawal treatment phase [68].

Benzodiazepines withdrawal

Mirtazapine can be also used as an adjunctive treatment for the management of benzodiazepine withdrawal symptoms including insomnia, depression and sleep myoclonus [69].

Stimulants

Amphetamines

The safety and efficacy of mirtazapine in treating amphetamine withdrawal were assessed using the total Amphetamine Withdrawal Questionnaire, and showed significant improvements in hyperarousal and the anxiety subscale scores, thus, lending some support to the hypothesis that mirtazapine may be an option in the management armamentarium of amphetamine detoxification treatment [70].

Cocaine

Mirtazapine was found to be also beneficial in improving sleep in patients with co-occurring depression and cocaine use disorder, however, it was not effective in reducing the frequency of cocaine use [71].

Cannabis

Until recently, no official definition of a cannabis withdrawal was listed in the official diagnostic nomenclatures; but with the publication of the DSM-5, a cannabis withdrawal syndrome is now recognized with defined criteria [5]. Different pharmacotherapies have been studied in cannabis withdrawal and of these, perhaps mirtazapine, has shown some promise in the specific treatment of cannabis withdrawal symptoms [72].

Autistic Disorder

Autistic Disorder (Autism) which is a neurodevelopmental disorder characterized by marked impairment in social interaction and communication along with restricted, repetitive, and stereotyped patterns of interests and behavior has been reclassified according to DSM-5 under the category of Autism Spectrum Disorders [5]. Its optimal treatment requires individualized tailored treatment plan that include educational interventions, speech and language therapy, and specialized behavioral interventions. Even with ongoing psychosocial and educational interventions, many individuals remain severely impaired due to associated symptoms of aggression, self-injury, hyperactivity, and interfering repetitive behavior. These behaviors are the ones most often designated as appropriate targets for pharmacotherapy. Mirtazapine showed modest effectiveness for the treatment of certain maladaptive behaviors associated with autistic disorder [73].

Mirtazapine Use in Medical Conditions

Treatment of nausea, emesis in cancer patients

Nausea, emesis and pain are very common and frequently distressing manifestations of various types of cancer. The recurrence of nausea and emesis, during cancer chemotherapy and during palliative cancer care, can significantly impair the quality of life and affect mood as well as the ability to experience pleasure. Mirtazapine, due to its 5HT3 antagonist properties, has been shown to have clinically observed anti-emetic and anti-nausea effects [74]. There is also some research evidence supporting its use in reducing symptoms related to cancer chemotherapy [74,75] as well as in cancer cachexia [76]. Its relatively favorable side effect profile makes it a viable treatment option, given the fact that cancer chemotherapy patients may already be exposed to significant side effects and drug interaction related to their multiple chemotherapeutic agents [77].

Treatment of sleep difficulty, weight loss in cancer, cachexia patients

Sleep disorders, weight loss and reduced appetite are frequently observed in cancer patients with depression. Mirtazapine improves appetite through H1 blockade, 5-HT2C antagonism and can help cachexic patients gain needed weight in addition to a rapid resolution of their initial, middle and late insomnia [77]. However, clinicians need to be aware that mirtazapine due to its norepinephrenergic activity at higher doses , could be associated with less sedation and reduced appetite and that should be taken into consideration when using mirtazapine in cancer patients with cachexia [76,77]. Because of some reports of agranulocytosis secondary to mirtazapine [12], caution should be exercised when using it in cancer patients, and further controlled trials would be required in this population.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a prevalent gastrointestinal disorder that affects 10% to 27% of the US population and is frequently associated with co-occurring psychiatric conditions especially depression [78,79]. Mirtazapine in addition to its effects on treating depression in patients with IBS it was found to decrease levels of gastrointestinal symptoms [80,81]. These beneficial effects of mirtazapine were attributed to its 5HT3 receptor antagonism, which could modulate visceral pain, colonic transit speed and gastrointestinal secretions [74]. Further studies would be needed to establish the potential therapeutic effects of mirtazapine in the overall treatment of patients with IBS even those without co-occurring depression.

Gastroparesis

Gastroparesis is a clinical disorder characterized by delayed gastric emptying in the absence of mechanical outlet obstruction and is manifested by upper gastrointestinal symptoms, including nausea, vomiting, postprandial fullness, early satiety, abdominal pain and bloating. Various therapies have been utilized for the treatment of gastroparesis including nutritional modifications, medications to stimulate gastric emptying, agents that reduce vomiting, in addition to endoscopic and surgical approaches. Mirtazapine was found to reverse recurrent postprandial discomfort, nausea, and vomiting, in a patient with refractory gastroparesis who did not respond to treatment with conventional prokinetics (erythromycin, metoclopramide, domperidone, perphenazine, itopride, bethanechol, and/or tegaserod)

and pyloric injection of botulinum toxin [82]. The use of mirtazapine may be a safer option for persistent gastroparetic symptoms in older patients, or for patients who are not ideal candidates for first-line therapies, and in cases where invasive therapies are not indicated [83].

Hyperemesis Gravidarum

Hypermesis gravidarum is a complication of pregnancy that is characterized by severe nausea and vomiting that could lead to weight loss and dehydration. Signs and symptoms may include vomiting several times a day and feeling faint. It is more severe than morning sickness and has been linked in severe cases, to life threatening risks for the mother or the growing fetus [84]. Some pregnant women with severe hyperemesis gravidarum that did not respond to conventional antiemetic agents showed an early rapid response to mirtazapine, with the resolution of emesis throughout the remainder of their pregnancies and consequently delivered healthy new born babies [84,85]. However, larger controlled studies are still needed to confirm the efficacy of mirtazapine in the treatment of pregnant patients with severe hyperemesis gravidarum.

Neurological Disorders

Temporal lobe epilepsy and co-occurring depression

Depression in temporal lobe epilepsy has been established as a frequent occurrence, and patients with temporal lobe epilepsy with depression often report a poorer quality of life on global assessments and are at an increased risk of suicide as compared to the general population [86]. Although various possible mechanisms for this significant comorbidity have been suggested, there is still little to guide a clinician in the recognition and management of depression in patients with temporal lobe epilepsy. In recent years, significant effort has been made to address these issues and provide a framework for diagnosis and management of depression in this population using various antidepressants, including mirtazapine [87].

Movement Disorders

Mirtazapine may be an effective therapy for patients who have tremor associated with Parkinson's disease, resting tremor, benign familial tremor (essential tremor) action tremor and for the treatment of levodopa-induced dyskinesias and other dyskinesias [2]. Clinicians prescribing mirtazapine need to be also aware akathisia of mirtazapine potential for inducing nocturnal movement disorders, such as periodic limb movement disorder [88].

Tension Headaches

Although the TCA amitriptyline is generally considered one of the first line treatments for tension type headache, mirtazapine has been shown to decrease the frequency, duration and intensity of tension headaches in some patients who did not respond to amitriptyline [89]. In contrast to amitriptyline, mirtazapine has the advantage of a more favorable side effect profile [90].

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a demyelinating central nervous system disease caused by reactivation of the JC virus (JCV). The disease course of PML is usually progressive and fatal. It can occur in immunocompromised patients, including those with acquired immune deficiency syndrome (AIDS), hematological malignancies, post-transplantation on immunosuppressive therapy and sarcoidosis. The combination treatment of cidofovir and mirtazapine, can lead to a significant improvement of neurological symptoms without measurable functional deficit in PML patients with sarcoidosis [63,91].

Progressive Multifocal Leukoencephalopathy associated with Polycythemia Vera

Patients with polycythemia vera who develop PML, when treated with mirtazapine, could remain neurologically stable, with resolution of their cerebral lesions, > 2 years after PML diagnosis [92].

Progressive multifocal leukoencephalopathy and human immunodeficiency virus infection (HIV)

Patients with HIV infection and PML treated with mirtazapine and mefloquine, could well tolerate the combined treatment and exhibit functional and cognitive improvement, however clinicians need to be aware that the specific effects of combined mirtazapine and mefloquine are difficult to discern in regard to mirtazapine primary effects on improving cognition or secondary effects of improving depressed mood and thus resulting in improved cognition [63].

Hot flashes

Some evidence does suggest that mirtazapine may reduce hot flashes in breast cancer survivors who are treated with tamoxifen [93]. Furthermore, mirtazapine has some benefits over some other antidepressants due to its minimal effect on the cytochrome oxidase enzyme CYP2D6 syatems, which metabolize tamoxifen that could lead to the reduction of its chemotherapeutic effects [94].

Sexual dysfunction

A considerable proportion of patients, or as many as 30 to 80 %, who are prescribed SSRIs or SNRIs antidepressants may experience sexual side effects manifested by reduced or poor sexual desire, erectile dysfunction, delayed ejaculation or anorgasmia [95]. These sexual side effects may result in poor quality of life, marital dissatisfaction and often lead to the discontinuation of antidepressants, and thus contribute to a risk of relapsing into recurrence of depression [96]. Some patients with depression who had discontinued SSRIs secondary to their sexual side effects, found mirtazapine to be significantly beneficial for treating the depression without the development of sexual side effects [97]. When mirtazapine is combined with an SSRIs or an SNRIs it was found to be beneficial in reducing their sexual side effects [2,98]. Mirtazapine can also used as an augmenting antidepressant in patients who are not improving while receiving an SSRIs and as such it leads to improvement in depression without the development of sexual side effects [99].

Mirtazapine Use in Children and Adolescents

Although mirtazapine is not approved for the treatment of children and adolescents it has been used in the treatment of social anxiety disorder and anorexia nervosa

Social anxiety disorder (social phobia)

Social phobia is characterized by fear or apprehension towards social or unfamiliar interpersonal situations, leading to active avoidance of these situations or significant distress and/or discomfort in such situations. This psychiatric condition has a peak age of onset in adolescence, and can be one of the most common anxiety disorders in children and adolescents, with a chronic and debilitating course, if left untreated. The use of mirtazapinee in the treatment of children and adolescents with social phobia may lead to an improvement and remission of the symptoms of social phobia, especially in the first few weeks of treatment [100]. Given the side effects of mirtazapine in precipitating significant weight gain clinicians need to constantly monitor the development of this side effects, which could worsen patients perception of their body image and also could lead to treatment discontinuation [100].

Adolescent anorexia nervosa

Anorexia Nervosa (AN) is an eating and feeding disorder that presents with weight loss, distorted body image, amenorrhea and sometimes with vomiting and loss of appetite, and when untreated, it can be associated with increased mortality risk. Given the complex nature of this disorder, medical comorbidities and accompanying treatment challenges, use of medication in this population requires careful consideration of various factors. The tolerability of mirtazapine, along with its propensity for weight gain, can make it an option worth considering in this patient population [49,101].

There may be other potential areas of mirtazapine use in this population including the treatment of sleep difficulties especially in children and adolescents receiving stimulants treatment for attention hyperactivity disorder [102].

Conclusion

Mirtazapine is a medication that has been approved by the FDA for the treatment of depression. Its unique receptor profile and mechanism of action, coupled with a relatively benign side effect profile, makes it suitable for a wide constellation of clinical conditions. Various studies have shown some beneficial effects in the treatment of many psychiatric and medical conditions. Many of these clinical conditions are complex, and pose significant morbidity. Mirtazapine's unique ability to improve sleep, and appetite, and to decrease nausea, anxiety, and to stabilize depressed mood; makes it a valuable treatment option. Its benign cardiac profile, low propensity for seizures, lack of sexual dysfunction and relative rapid onset of action may make it preferable to use of some other psychotropic medications, particularly in medically complex or special populations.

Despite the favorable clinical experience and the encouraging results from the many studies that have tested mirtazapine's beneficial effects, large, randomized controlled clinical trials need to be conducted to further evaluate its efficacy in the treatment of other the diseases and symptoms for which it is often used in clinical practice, many of which are discussed in this review. Such studies would also need to demonstrate the risk/benefit ratio for the many non- FDA approved conditions for which mirtazapine has been prescribed. It is possible that further studies on mirtazapine could further expand the areas where its unique receptor profile could be taken advantage of, allowing greater treatment options in many complex conditions.

It is hoped that this review will provide mental health and primary care providers with the information that they need to become familiar with prescribing mirtazapine as an option for various ""off label"" psychiatric and medical conditions, particularly in clinical instances where FDA approved treatments have not achieved their intended therapeutic effectiveness ,or were not well tolerated by patients .

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending,or royalties.

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