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A Review of the Literature of Mirtazapine in Co-Occurring Depression and an Alcohol Use Disorder

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Abstract

Background—Prior medication studies involving individuals with major depression in combination with an alcohol use disorder (MDD/AUD) have mainly focused on SSRI and tricyclic antidepressants, with generally ineffective results. Consequently, effective treatments for that common comorbid condition remain elusive. Mirtazapine is an antidepressant medicine with a unique pharmacological profile, whose effectiveness for treating non-comorbid depression reportedly may exceed that of SSRIs.

Objective/Methods—We now review the published literature regarding the tolerability and efficacy of mirtazapine for the treatment of the depression and the pathological alcohol ingestion of individuals with co-occurring MDD/AUD, including a review of four of our own small studies and two studies conducted outside the United States.

Results/Conclusions—The findings of these studies suggest that mirtazapine is well tolerated among persons with comorbid MDD/AUD. Results also provide some evidence of efficacy for mirtazapine for decreasing the level of depression of persons with co-occurring MDD/AUD, and suggest that decreases in depression may occur relatively quickly after starting treatment, but provide no evidence of effectiveness for decreasing the level of alcohol ingestion. Large-scale double-blind, placebo-controlled studies are warranted to further clarify the tolerability and efficacy of mirtazapine among individuals with MDD/AUD.

Keywords

Mirtazapine; Comorbid; Major depression; Alcohol use disorder

Introduction

Previous studies have shown no clear evidence of efficacy for SSRI or tricyclic antidepressant medicines for treating the common comorbid condition of MDD/AUD [1–3]. Consequently, effective treatments for that co-occurring condition remain elusive. However,

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Lovieno and colleagues [4] noted a conspicuous lack of studies involving a number of newer antidepressants, such as mirtazapine, for treating various comorbid populations. Consequently, the usefulness of those medicines for treating MDD/AUD is currently unclear.

Mirtazapine is a tetracyclic antidepressant medication used primarily for treatment of depression, though it is also sometimes used for treating anxiety or sleeplessness or for other indications. Mirtazapine is approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder. It is unique in its pharmacological profile among the currently available antidepressants, unrelated to tricyclic antidepressants and SSRIs. Mirtazapine is different from SSRIs and some other antidepressant medications in that it is not a reuptake inhibitor [5]. Mirtazapine combines two synergistic mechanisms of action, including enhancement of both serotonergic and noradrenergic neurotransmission. Mirtazapine is one of the few noradrenergic and specific serotonergic antidepressants (NaSSAs). There is evidence that antidepressant medications with a dual mechanism of action affecting both the serotonin and norepinephrine systems, such as mirtazapine, may be more effective under some circumstances than those with only a single neurotransmitter action, such as the SSRIs [5]. Findings from a recent meta-analysis [6] suggest that mirtazapine may demonstrate a stronger effect for decreasing depressive symptoms than other antidepressant medications. Mirtazapine has been reported to demonstrate a more rapid onset of action than SSRI antidepressants, with a significant difference in favor of mirtazapine over placebo being seen at various time points within the first four weeks of treatment [7,8,9], with some studies showing a significant difference from placebo as early as week 1 of treatment [10].

Findings from preclinical studies involving rats and published case studies in humans suggest that mirtazapine therapy may contribute to successful outcomes across a number of substance use disorders, including alcohol use disorders, amphetamine dependence, and other substance use disorders [11,12]. Consequently, those recent reviews have suggested that preliminary findings suggest a promising role for mirtazapine in addiction pharmacotherapy. However, a large scale clinical trial assessing the utility of mirtazapine in the treatment of substance use disorders has not yet been conducted [12].

Mirtazapine is typically well tolerated, with few medication side effects, though its use has been reported to be associated with sedation and weight gain [7,13]. Mirtazapine use is not typically associated with sexual dysfunction that may occur with SSRI medications and other antidepressants. Mirtazapine is typically associated with a low drop-out rate [13].

Methods

We reviewed the published literature regarding the tolerability and efficacy of mirtazapine for the treatment of the depression and the pathological alcohol ingestion of individuals with MDD/AUD, including a review of four of our own small studies and two studies conducted outside the United States, in order to elucidate the tolerability and efficacy of mirtazapine in that comorbid population.

Results

An acute phase open label pilot trial

The authors of the current manuscript recently conducted a first American open label medication trial investigating the acute phase efficacy of mirtazapine for decreasing the depression and the pathological alcohol ingestion of adults with co-occurring MDD/AUD [14]. Diagnoses were made using the Mini-International Psychiatric Interview (MINI) [15]. Seven men and five women participated in that pilot study, including nine Caucasians, one African American, one Native American, and one Asian American. The average age of trial participants was 36 years of age. Depression and drinking behaviors were both prominent at the time of the baseline assessment. Findings from that study suggest robust acute phase efficacy for mirtazapine for decreasing both the depression and the pathological alcohol ingestion of that population. Specifically, depression decreased from 31.8 to 8.2 on the Beck Depression Inventory [16], a 74.0% decrease ($p<0.001$), and alcohol ingestion decreased from 33.9 to 13.3 drinks per week on the Timeline Follow-Back Scale [17], a 60.8% decrease ($p<0.05$). Mirtazapine was well tolerated during that study. However, the investigators of that study could not exclude the possibility that the MET therapy [18] used during the study had contributed to the clinical improvements noted during the study or that placebo effect had contributed to the results. Also, the investigators could not determine whether the clinical improvements that had been observed continued beyond the 8-week acute phase study.

A long-term (two year) follow-up study of subjects from an open label pilot trial

Until recently, no studies had evaluated the longer-term effectiveness of mirtazapine for treating the depression or the pathological alcohol consumption of individuals with comorbid MDD/AUD. In 2013, the authors of the current manuscript reported the results of a first long-term (two-year) naturalistic follow-up study [19] of mirtazapine in individuals with co-occurring MDD/AUD. That study involved persons who had formerly participated in our acute phase mirtazapine trial described immediately above, and who had then received naturalistic treatment provided by their local non-protocol-related clinicians thereafter. The investigators hypothesized that mirtazapine would manifest long-term within-group efficacy for decreasing both the depression and the level of alcohol ingestion of those individuals. That long-term follow-up study utilized the same study instruments that had been used in the acute phase trial. Ten of the twelve individuals who had previously participated in the acute phase medicine trial subsequently entered the long-term follow-up study.

During the two-year course of the study, the improvements that had been observed during the acute phase study in depression and in level of alcohol use were noted to have persisted. Specifically, at the follow-up evaluation, the large magnitude improvements in depression as measured by the Beck Depression Inventory (BDI) and alcohol ingestion as measure by the Time-Line Follow-Back (TLFB) continued, as compared to baseline levels ($p<.01$). Only two of the participants met diagnostic criteria for MDD on structured interview at the two-year follow-up rating session, while all ten had demonstrated that diagnosis at the baseline rating. BDI scores had decreased from 30.7 (± 8.59) at baseline to 6.8 (± 5.71) at the end of the acute phase, and then increased only slightly to 9.7 (± 6.65) at the 2-year follow-up

rating session ($t=5.4$; $p<.001$, when comparing baseline to follow-up level). Six of the 10 individuals reported using antidepressant medicine at some point during the follow-up period, including three who reported using mirtazapine and three who reported using various SSRI medications. At the baseline rating session, only three of the ten individuals were employed, while at the follow-up rating session seven were employed, suggesting an improvement in level of functioning associated with the decreased levels of depression and alcohol ingestion. At the baseline rating session, 4 of the 10 subjects met diagnostic criteria for dysthymic disorder, while at the follow-up visit, only one individual met diagnostic criteria for that disorder. At the baseline rating session, the average number of DSM-IV criteria for dysthymic disorder was 3.1, while at the follow-up assessment the average number of DSM-IV criteria for that disorder had fallen to 0.4, which was a significant decrease ($p=0.04$). At the baseline rating session, all 10 individuals met diagnostic criteria for alcohol dependence, while at the follow-up visit, only 5 of those persons met diagnostic criteria for that disorder. Drinks per week decreased from 37.9 (± 16.73) at the baseline rating session to 16.96 (± 12.93) at the conclusion of the acute phase trial, and then stayed almost the same at 16.1 (± 10.59) at the follow-up visit. ($t=3.13$; $p=0.012$). Those long-term results suggested persisting efficacy for mirtazapine for decreasing the depression and the level of alcohol ingestion of persons with co-occurring MDD/AUD. However, the investigators of that study could not exclude the possibility that other treatments such as MET therapy or SSRI antidepressants or placebo effect may have contributed to the clinical improvements noted at the time of the two-year follow-up assessment. A study utilizing a double-blind, placebo-controlled methodology would be needed to elucidate the effectiveness of mirtazapine among individuals with MDD/AUD.

A double-blind, placebo-controlled pilot study involving adults

In a subsequent study, our research group conducted a first double-blind placebo-controlled pilot study to assess the efficacy of mirtazapine for decreasing both the depression and the pathological alcohol ingestion of individuals with comorbid MDD/AUD [20]. That study used very similar methodology to our open label studies described immediately above, except that a double-blind placebo-controlled methodology was used rather than an open label methodology, and the length of the study was 12 weeks rather than 8 weeks. All persons in both treatment groups received motivational enhancement therapy. Fourteen individuals participated in that medicine trial, including 10 (71%) men and 4 (29%) women. Half of those individuals were Caucasian and half were African American. The average age of those who participated in the clinical trial was 41.3 years ($SD=8.8$). Within-group tests in the mirtazapine group demonstrated a trend for a decrease in depression ($p<0.07$) as early as week 1, with a 32% decrease in BDI depression symptoms noted by the week 1 rating in the mirtazapine group. A significant within-group decrease in depression among members of the mirtazapine group was noted at week 2 of the study (47% decrease, $p=0.01$), and a significant within-group decrease in level of depression (compared with baseline levels) was also noted at all subsequent assessments (weeks 3, 4, 6, 8, 10, and 12) during the 12-week study. In contrast, no significant within-group decrease in depression symptoms was noted in the placebo group until week 8, with no within-group decreases in depressive symptoms being noted in the placebo group at weeks 2, 3, 4, or 6. Thus, a within-group improvement in depression symptoms was noted substantially earlier in the mirtazapine group than in the

placebo group (week 2 versus week 8), which is consistent with previous reports of a rapid onset of action of mirtazapine [7,8,9,10], and that improvement was sustained throughout the remainder of the medication trial. Both treatment groups showed significant decreases in depression by the end of the clinical trial (week 12), but no between-group differences in depression was noted at any time point, and no significant differences in level of alcohol ingestion were noted at any time point, possibly because of limited sample size. Thus, the trial results were mixed as to whether mirtazapine demonstrated a therapeutic effect on depression symptoms in persons with MDD/AUD, though it appeared that the mirtazapine group demonstrated an earlier onset of antidepressant activity. In contrast, no therapeutic effect for mirtazapine was shown for treating excessive alcohol consumption of that comorbid population.

A double-blind, placebo-controlled pilot study involving young adults/older adolescents

Alcohol misuse is an especially concerning problem among young adults (the 18 to 25 year old age group), according to the National Survey on Drug Use and Health [21]. A small double-blind, placebo-controlled pilot study involving mirtazapine in young adults is currently underway to assess whether the findings noted in recent studies involving middle-aged and older adults with MDD/AUD can be applied to younger adults and late adolescents. Findings from a younger age population are needed, because adolescents and young adults have been shown to have a lower response rate and higher rate of side effects (including suicidality) than older persons treated with SSRI antidepressants and other antidepressants [22]. To date, only one small pilot study of mirtazapine in MDD/AUD young adults has been conducted [23]. The methodology of that study was the same as the methodology for the double-blind, placebo-controlled study in adults with MDD/AUD described immediately above. To date, a total of 7 subjects have entered into that ongoing study. Those subjects included 4 males and 3 females, with 4 Caucasians and 3 African Americans. Final outcome results are not yet available for this ongoing study, because the blind has not yet been broken, and the study remains ongoing. However, it can be noted that all individuals participating in the study to date have demonstrated decreases in both depression symptoms and in level of alcohol consumption. None of the young adult subjects in that study has demonstrated significant medication side effects or paradoxical increases in suicidal symptoms or other types of adverse events. Larger studies will be needed to clarify the tolerability and effectiveness of mirtazapine among young adults and older adolescents with MDD/AUD.

Two Trials conducted outside the United States

Two trials involving mirtazapine in MDD/AUD subjects have been conducted outside the United States. In the first of those two trials, Yoon et al. [24] conducted an open label naturalistic study of mirtazapine in South Korea. A total of 184 adults were recruited into the study and 128 of those (69.6%) completed the 8-week study. The findings of that open label study showed significant within-group improvement in level of depression. In the second of those two trials, Altintoprak et al. [25] conducted a double-blind placebo-controlled trial of mirtazapine in adult subjects with MDD/AUD in his study conducted in Turkey. Forty-four individuals participated in that study. The findings of that clinical trial demonstrated superiority for mirtazapine over placebo for decreasing the depression of persons with

MDD/AUD, as measured on the Hamilton Depression Rating Scale. However, neither of those studies conducted outside the United States evaluated the level of alcohol ingestion. Consequently, the effectiveness of mirtazapine for lowering the level of alcohol ingestion in individuals with MDD/AUD could not be assessed in those two studies.

Discussion

This manuscript reviewed the published literature regarding the tolerability and efficacy of mirtazapine for the treatment of the depressive symptoms and the pathological alcohol ingestion of individuals with co-occurring MDD/AUD, including a review of four of our own studies involving mirtazapine in MDD/AUD. This manuscript also reviewed two studies involving mirtazapine versus placebo in persons with MDD/AUD that were conducted outside the United States (in South Korea and Turkey). Results from our recent acute phase open label study suggest robust acute phase efficacy for mirtazapine for decreasing both the depression and the drinking of adults with MDD/AUD. Results from our long-term open label study of mirtazapine in MDD/AUD suggest persisting effectiveness for mirtazapine for decreasing both the depression and the alcohol ingestion of persons with MDD/AUD, though a response to motivation enhancement therapy or a placebo response could not be excluded. Results from our very recent double-blind placebo-controlled pilot study suggest early onset of within-group efficacy for mirtazapine for decreasing the depression symptoms of individuals with co-occurring MDD/AUD, and that improvement persisted throughout the remainder of the study. However, that placebo-controlled trial found no evidence of within-group efficacy for mirtazapine or efficacy for mirtazapine versus placebo for decreasing the level of alcohol ingestion of that comorbid population. Results from a recent small study involving mirtazapine versus placebo in young adults with MDD/AUD suggest that mirtazapine is well tolerated in that population, and suggest that the efficacy and the side effect profile of mirtazapine is similar in that younger age group as compared to that seen in middle aged and older adults. Results from the studies in South Korea and Turkey were consistent with the more recent studies conducted in the United States in suggesting efficacy for mirtazapine for decreasing the depressive symptoms of individuals with MDD/AUD, and suggesting that mirtazapine is well tolerated in persons with MDD/AUD. However, conclusions regarding the efficacy of mirtazapine for decreasing level of alcohol consumption could not be made from the studies in South Korea and Turkey because level of alcohol ingestion was not assessed in those two studies.

Mirtazapine was well tolerated in all of those studies, suggesting that mirtazapine is relatively safe for use in treating persons with co-occurring MDD/AUD. The results of those studies also suggest sustained efficacy for mirtazapine for decreasing the level of depression symptoms of persons with co-occurring MDD/AUD, and demonstrate that the decrease in depressive symptoms tends to occur soon after starting mirtazapine, suggesting a rapid onset of action of mirtazapine within the first week or two of starting that medication. That rapid onset of action noted in the studies involving comorbid samples reviewed in the current manuscript is consistent with previous reports of a rapid onset of action for mirtazapine among persons with major depression alone. Specifically, a significant decrease in depressive symptoms was noted as early as one week or two after starting the medication in the reports reviewed in the current manuscript involving comorbid samples, which is similar

to the time frame of treatment response noted by Quitkin et al. [10] involving non-comorbid single diagnosis populations treated with mirtazapine. However, mirtazapine did not show any evidence of efficacy for decreasing the level of alcohol consumption of that comorbid population. Thus mirtazapine, which is marketed as an antidepressant medication, appears to be more effective for decreasing depressive symptoms than for decreasing level of alcohol ingestion of individuals with co-occurring MDD/AUD. It is also noteworthy that decreases in level of depression noted in the studies involving mirtazapine that were reviewed in the current manuscript were generally more robust and more rapid than the improvements noted in our own previous studies involving SSRI antidepressants in comorbid populations [26,27,28]. Thus, it is possible that mirtazapine demonstrates a more robust therapeutic effect than other antidepressant medications for decreasing the depressive symptoms of persons with co-occurring disorders. Large double-blind studies and large studies comparing mirtazapine to other antidepressant medications would be needed to definitively clarify the efficacy, the time course of treatment response, and the side effect profile of mirtazapine versus placebo and versus other antidepressant medications in persons with various co-occurring disorders.

The results of the current review should be interpreted in light of some limitations. First, the sample size of the studies being reviewed was generally limited. Also, two of the studies did not assess the level of alcohol ingestion. In addition, a study design involving a placebo control group was utilized in only three (half) of the studies. Large-scale double-blind, placebo-controlled studies appear to be warranted to further clarify the tolerability and efficacy of mirtazapine in individuals with MDD/AUD.

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Abbreviations

MDD	Major Depressive Disorder
AUD	Alcohol Use Disorder

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