

Relationship between mirtazapine dose and incidence of adrenergic side effects: An exploratory analysis

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Abstract

Introduction: Mirtazapine is an antidepressant with US Food and Drug Administration approval for management of major depressive disorder. Low doses of mirtazapine are often used for management of insomnia, with higher doses expected to provide more noradrenergic effect, and thus a higher degree of activation. If so, use of higher doses at bedtime may not be advisable and may worsen certain neuropsychiatric symptoms. No studies have been performed to evaluate these outcomes.

Methods: This study consisted of a retrospective review of data submitted to the US Food and Drug Administration's Adverse Event Reporting System from January 1, 1995, to August 1, 2015. Cases that were deemed by study authors to represent activation of the noradrenergic system, and for which other confounders could not be identified, were included in the final analysis. The frequency of each specific adverse event was evaluated based on dose and compared to recent prescribing rates to determine if likelihood of a side effect increased with higher dose.

Results: The study identified 308 incidences of anxiety, agitation, delusion, hallucination, hypertension, insomnia, nightmare, or tachycardia. After controlling for frequency of prescribing at a given dose, there was a statistically significant increase in rates of tachycardia which correlated with dose. However, after correction for multiple comparisons, results were no longer significant.

Discussion: This study failed to support the hypothesis that mirtazapine is more activating at higher doses and appears to support the safety of increasing dose without increasing risk of noradrenergic side effects. Prospective studies will be necessary to confirm these findings.

Keywords: adverse drug reaction, depression, mirtazapine, posttraumatic stress disorder

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Introduction

Mirtazapine is a therapeutic agent that received initial US Food and Drug Administration (FDA)¹ approval for treatment of major depressive disorder on June 14, 1996. Since then, its off-label use has spread to treatment of other disease states, such as insomnia, generalized anxiety disorder, and posttraumatic stress disorder (PTSD).^{2,3} The mechanism of action of mirtazapine is unique. It appears to exert its therapeutic effect via an

overall increase in serotonin, norepinephrine, and dopamine levels, although not via the traditional blockade of reuptake transporters.^{4,5} Instead, it acts to modulate certain receptors that regulate levels of each of these neurotransmitters. For example, blockade of α_2 adrenergic heteroreceptors on serotonergic neurons in raphe nuclei results in increased serotonin release, whereas blockade of the presynaptic α_2 adrenergic autoreceptors located in the locus coeruleus increases release of norepinephrine.⁶⁻⁸ Furthermore, blockade of α_2 adrenergic heteroreceptors increases dopaminergic activity in cortical regions.⁵ Mirtazapine has its highest affinity for histaminergic H_1 receptors and serotonergic $5HT_{2A}$ receptors ($K_i = 0.14$ and 16 , respectively).⁸ Blockade of H_1 provides additional sedating and anxiolytic properties, whereas blockade of $5HT_{2A}$ receptors provides increased dopaminergic activity.^{7,9-11} Mirtazapine has been shown to exhibit lower affinity for α_2 receptors ($K_i = 141$).⁸ However, this is based on analysis of human cortical tissue and thus may not necessarily translate to other brain regions or fully represent the activity of the drug in the human body.^{8,12,13}

In the clinical setting, it is assumed that such properties result in sedation at lower doses and less sedation at higher doses, as more α_2 receptors become blocked and provide more of an activating effect through dopaminergic and noradrenergic signaling.¹⁰ The exact dose at which this occurs is not well delineated, nor are the effects on sedation conclusive. The few available data to support this are first based on comparisons between rates of sedation in European and US approval studies, with authors noting the difference in average dose and hypothesizing that this distinction was the source of the varying rates of sedation.¹⁰ There is additionally some evidence from the work of Grasmäder and colleagues,¹⁴ who reviewed the plasma levels and side effects of 45 patients receiving mirtazapine in a clinical setting. They noted a weak, inverse relationship between mirtazapine concentration and sedation. Low plasma concentrations were also associated with increased duration of sleep, although this effect did not persist beyond the first week.

These α_2 adrenergic receptor effects may have implications when applied to other disease states. Krystal and Neumeister¹⁵ have identified α_2 blockade as a potential modulator of PTSD symptoms and as an animal model of PTSD itself. There are case reports and anecdotal evidence alike supporting use of α_2 agonists (ie, clonidine or guanfacine) as alternatives to the α_1 blocker prazosin for treatment of PTSD-related nightmares.^{15,16} Given this, it would seem possible that mirtazapine's α_2 blockade provides concern when being used for treatment of PTSD and insomnia due to PTSD-related nightmares.¹⁷ Of note, the 2017 Veterans' Affairs/Department of Defense clinical practice guideline for the management of PTSD and acute stress disorder no longer includes mirtazapine as having a

recommendation for use (level B evidence), citing instead that there is insufficient evidence for or against use at this time.¹⁸ The stance is also supported by 2 other reviews but is in contrast to a recent network meta-analysis affirming its efficacy.¹⁹⁻²¹ A pharmacovigilance report²² was published in 2003 and described 50 cases of nightmares attributed to mirtazapine. However, doses were not provided. Thus, given its widespread use for insomnia, dosing guidance would be ideal in order to determine whether higher doses are more or less problematic.

Objectives

The goal of the current study was to determine whether activating side effects have been reported to the FDA's adverse event reporting as attributed to mirtazapine and, if so, at which doses. These doses would then be compared to rate of reporting of a given adverse drug reaction (ADR) to determine whether a relationship existed between dose and noradrenergic activity, using incidence of activating side effects as a surrogate marker.

Methods

This was a retrospective review of pharmacovigilance reporting of mirtazapine through the FDA's Adverse Event Reporting System (FAERS) from January 1, 1995, to August 1, 2015. The FAERS database is a collection of adverse events that is voluntarily reported to the FDA by health care providers, consumers, and manufacturers.²³ Each case report is given a unique case number upon submission to the FDA in order to maintain the confidentiality and privacy of individuals. These cases included specific descriptors. To capture any activating effects reported to the FDA, authors agreed upon prespecified search terms related to noradrenergic stimulation via α_2 antagonism. As a result, outcomes of interest included any incidences of abnormal dreams, anxiety, agitation, delusion, hallucination, hypertension, insomnia, nightmare, or tachycardia that resulted in an ADR to be submitted to the FDA between the dates listed above, for which mirtazapine was listed as a causative agent and a dose within the range of 3.75 and 90 mg was provided (Figure). Cases that listed one or more of these outcomes were reviewed by 1 of 3 investigators (M.S., A.C., or N.V.); any cases determined to be of questionable causality were then reviewed by all 3 investigators. Any adverse reactions that were reported outside of this time frame or were determined by the study investigators to be related to other factors (acute intoxication, withdrawal from a substance, serotonin syndrome) were excluded from the data, as were cases outside the age range of 18 to 65 years. Patients currently taking other psychotropic medications or those with known risk of similar side

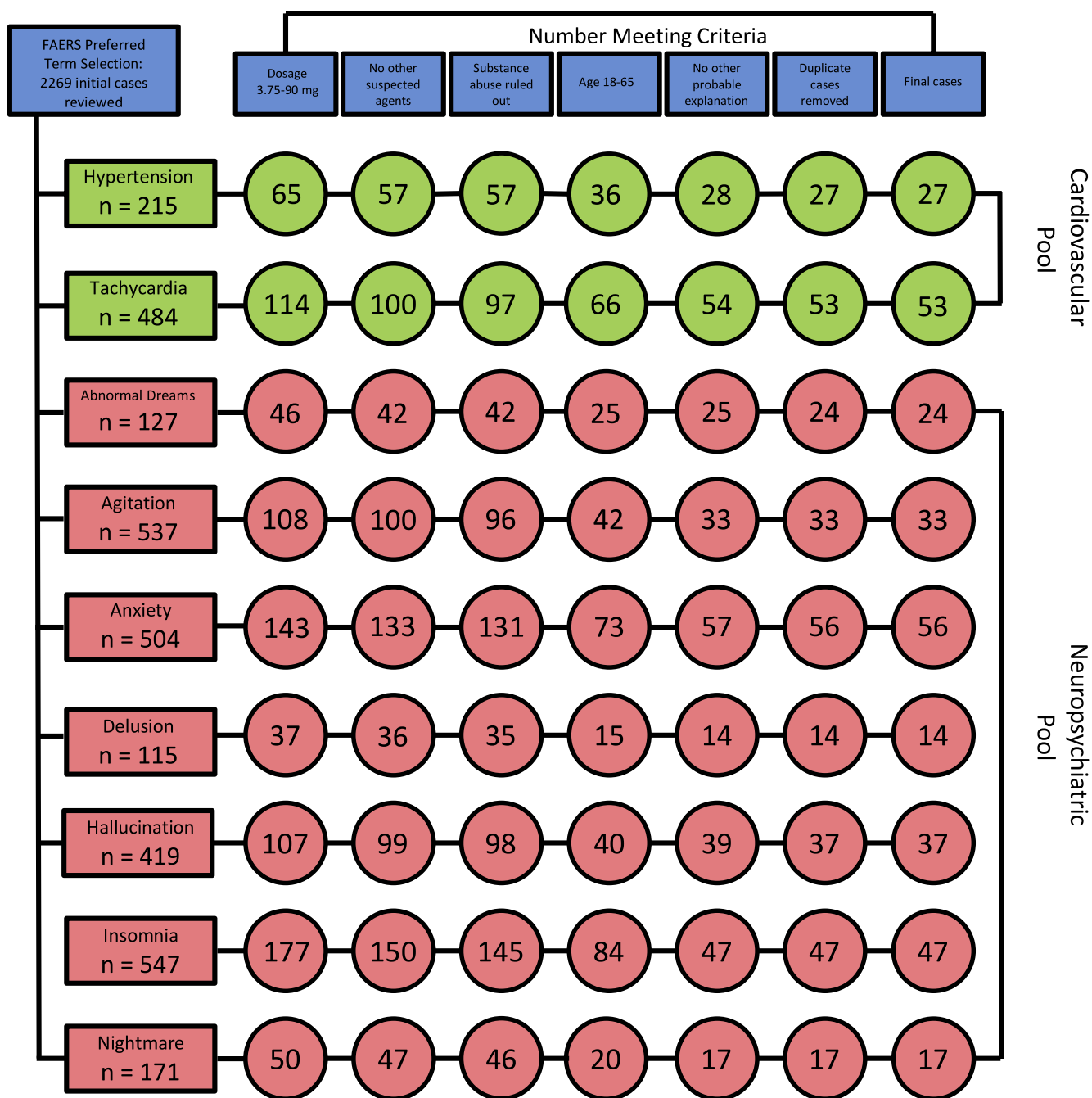


FIGURE: Flow of cases associated with mirtazapine, from initial review to inclusion within final analysis

effects, such as efavirenz, interferon, montelukast, prednisone, dextromethorphan, stimulants, cocaine, alcohol, or opioids, were excluded.²⁴ Cases of attempted suicide or death by suicide were also excluded, given that those doses were unable to be quantified. Once the data were catalogued, descriptive statistics were used to determine whether incidence of a given side effect could be correlated to increasing dose. To control for the fact that increased incidence of side effects may be solely a function of increased prescribing rates, US prescribing

data were obtained and χ^2 tests were performed to analyze the data.

Within the United States, the Medical Expenditure Panel Survey (MEPS) is the primary source of data regarding health care use. Data are collected on a representative sample of households nationwide, estimated as ~15 000, and conducted via telephone on an annual basis.²⁵ Utility of MEPS data for research purposes has already been established.²⁶ Using household survey results, pharma-

TABLE 1: Cases stratified by mirtazapine dose and reported adrenergic side effect

	Average Dose, mg	Median Dose, mg	Dose <15 mg, n	Dose = 15 mg, n	Dose = 30 mg, n	Dose >30 mg, n	Total Cases, n
Abnormal dreams	23.1	15	0	13	9	2	24
Agitation	24.6	30	2	12	17	2	33
Anxiety	23.6	15	4	26	19	7	56
Delusion	30	30	2	4	4	4	14
Hallucinations	23.9	15	4	15	12	6	37
Hypertension	33.6	15	1	9	8	9	27
Insomnia	26.8	15	2	19	15	11	47
Nightmares	21.2	15	2	8	6	1	17
Tachycardia	29	30	1	15	27	10	53

cies are then contacted in order to obtain data, including National Drug Code, medication name, date filled, quantity and dose, and payment source.²⁷ Using data program R version 3.4.2²⁸ and existing data^{29,30} available through the MEPS program, records were obtained for all individuals in the sample who were prescribed mirtazapine in calendar year 2013, because this was the most recent year of survey data available. There were no adjustments for patients taking half tablets or altering doses on their own; an assumption was made that written doses provided per pharmacy records were correct. Although the data are not designed to provide national estimates, they were able to be used to determine the ratio of doses prescribed at 7.5, 15, 30, and 45 mg. No doses above 45 mg were recorded in the MEPS sample, and thus statistical analysis was unable to be performed for cases reported at these doses. The relative prescribing rate at each dose (7.5, 15, 30, and 45 mg) was compared to the number of individuals reporting a given ADR at each dose, using Pearson χ^2

coefficients to determine whether frequency of that ADR was associated with dose.

Results

During the time period from January 1, 1995, to August 1, 2015, a total of 14 719 adverse reactions were reported to the FDA listing mirtazapine as an active ingredient. Using initial search terms to identify the specific adverse events of interest thought to be related to excess adrenergic activity, 2269 cases were identified (Figure). After removing cases that met exclusion criteria, a total of 308 cases were included in final analysis and categorized by dose (Table 1). No association was found between dose of mirtazapine and likelihood of experiencing abnormal dreams, agitation, anxiety, delusions, hallucinations, hypertension, insomnia, or nightmares (Table 2).

We noted a linear association between dose and rate of tachycardia ($P=.043$). However, after using Bonferroni correction (setting α to .0056 to account for multiple

TABLE 2: Relationship between mirtazapine dose and incidence of adrenergic side effects

Symptom	Likelihood Ratio ^a χ^2 (P Value)	Pearson ^a χ^2 (P Value)	Linear by Linear Association, Z Statistic (P Value)
Abnormal dreams	2.358 (.502)	1.480 (.687)	−0.298 (.766)
Agitation	5.541 (.136)	4.939 (.176)	−0.424 (.672)
Anxiety	1.872 (.599)	2.330 (.507)	−0.958 (.338)
Delusion	3.737 (.291)	6.389 (.094)	−0.405 (.685)
Hallucinations	4.592 (.204)	6.484 (.090)	−0.380 (.704)
Hypertension	1.874 (.599)	2.236 (.525)	0.982 (.326)
Insomnia	3.752 (.290)	4.475 (.215)	1.191 (.234)
Nightmares	2.635 (.451)	3.690 (.297)	−1.298 (.194)
Tachycardia	6.520 (.089)	6.415 (.093)	2.028 (.043) ^b

^aDegrees of freedom = 3.

^bWhen Bonferroni correction applied, results no longer significant.

comparisons and 9 separate primary end points), the result was not statistically significant.

Discussion

After excluding cases where mirtazapine was not a suspected cause or for which there were duplicate entries, a total of 308 cases of interest likely attributable to mirtazapine were identified out of 14 719 adverse events reported to the FDA regarding this agent. Although the overall rates of various neuropsychiatric/adrenergic side effects from mirtazapine were low within the population, this is in line with data collected by Biswas and colleagues,²² who identified, for example, 15 cases of abnormal dreams likely caused by mirtazapine, out of a total population of 13 554. Similarly, they found 14 cases of agitation, 10 cases of insomnia, 7 cases of worsening anxiety, and 4 cases of palpitations.

Despite the low numbers, actual rates may be much higher. There is a significant body of literature supporting the concept that spontaneous reporting, the method by which most surveillance systems collect their data, results in underreporting of adverse effects.^{31,32}

Rather than reviewing each year separately to examine prescribing rates and adverse event reporting rates within that same year, we pooled all of the adverse events for a specific dose across all years within the study period and compared them to prescribing rates within a given year, 2013. Although it is possible that the relative prescribing rates at each dose may vary from year to year, from an examination of year 2000 data there was little variance other than an increase in prescribing at the 45-mg dose. Thus, we feel that we can provide a reasonable estimate using data from a single year.

Although the receptor activity profile of mirtazapine has led to its use in the treatment of insomnia, we have previously raised concern for potential adverse effects, particularly a dose-dependent increase in the risk of nightmares.³⁷ This study of cases contained in the FDA's Adverse Event Reporting System where mirtazapine could be reasonably linked to a reported adverse effect found no relationship between dose of mirtazapine and incidence of nightmares. In addition, the incidence of abnormal dreams, agitation, anxiety, delusion, hallucination, hypertension, and insomnia were also not found to be related to dose. This result does not rule out mirtazapine having an effect on nightmares, because this has been previously identified through pharmacovigilance reporting.²² Rather, the effect may not be dose dependent, as it has previously been noted at doses of 7.5 and 15 mg.³³ In addition, the effect may be modulated by receptor activity other than α_2 adrenergic antagonism. Mirtazapine also has 5HT_{2A}

antagonist properties that could potentially negate the nightmare-promoting effect of the α_2 adrenergic antagonism, an effect previously described with cyproheptadine.^{34,35} As such, further study is required to justify the therapeutic role of mirtazapine in PTSD patients.

Our findings stand in general agreement with those of Grasmäder and colleagues,¹⁴ who reported an inverse relationship between dose and sedating effect that disappeared after 1 week of use. We did not account for duration of use prior to reporting of the adverse effect because we did not have this information available for most cases. However, when available the duration of use within our population ranged from 1 to 584 days.

A relationship between mirtazapine dose and cardiovascular adverse effects has been previously documented. For example, Bremner and colleagues³⁶ described 8 cases of mirtazapine overdose. Other than central nervous system depression, the most common adverse effect was tachycardia. Berling and Isbister³⁷ identified 89 cases of overdose solely on mirtazapine, with 29 experiencing tachycardia and 32 noting hypertension. None experienced delirium or other neuropsychiatric effects other than altered mental status. LoVecchio et al³⁸ and Waring et al³⁹ report similar findings. As a retrospective study of pharmacovigilance reporting, this study is limited by observational error in the FDA's Adverse Event Reporting System. However, the distribution of doses reported to FAERS is consistent with data obtained from MEPS and previous pharmacovigilance studies, indicating that it is likely representative of the larger population.^{22,29}

Conclusion

Despite the general understanding that α adrenergic effects of mirtazapine occur in a dose-dependent manner, there was no evidence for dose-dependent adverse effects other than a trend toward increased rate of tachycardia with higher doses. The incidence of adverse effects at a given dose therefore appears to reflect prescribing patterns, in that doses prescribed more frequently would have greater incidence of adverse effects. This includes no evidence of a dose-dependent effect on insomnia, nightmares, or other neuropsychiatric effects. A possible alternative explanation is that our data set simply lacked sufficient sensitivity to find a relationship. However, this alternative interpretation does not explain the detection of a dose-dependent effect of mirtazapine on the incidence of tachycardia.

These results seem to indicate that doses may be titrated upward at bedtime with low concern for insomnia or activating effects. There remains a safety signal for neuropsychiatric effects that is not necessarily dose

dependent; thus, continued caution should be exercised when prescribing to individuals with PTSD.

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