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Review Article

Mirtazapine-associated movement disorders: A literature review

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Abstract

Mirtazapine (MTZ) is an atypical antidepressant approved by the FDA, which mechanism of action involves the antagonism of alpha-2, H1, 5-HT2A, 5-HT2C, and 5-HT3 receptors. In this context, the aim of this literature review is to evaluate the clinical epidemiological profile, pathological mechanisms, and management of MTZ-associated movement disorders (MDs). Relevant reports of six databases were identified and assessed by two reviewers without language restriction. Fifty-two reports containing 179 cases from 20 countries were assessed. The mean age was 57 year (range, 17–85). The majority of the individuals were female (60%) and of European origin. The mean time from MTZ start to symptom onset was 7.54 days; the time from management to MD improvement was within one week in 82.60% of the individuals. The MDs associated with MTZ were 69 restless legs syndrome (RLS), 35 tremors, 10 akathisia (AKT), 9 periodic limb MD, 6 dystonia, 4 rapid eye movement sleep behavior disorders, 3 dyskinesia, 2 parkinsonism, and 1 tic, and in the group not clearly identified, 18 restlessness, 15 hyperkinesis, and 1 extrapyramidal symptom. In the literature, the majority of the reports lack important information about the neurological examination. The management should be the MTZ withdrawal, except in RLS that other options are possible. In AKT, the MTZ should not be rechallenge, and if available, the prescription of a benzodiazepine may reduce recovery time.

Keywords: *Drug-induced, Mirtazapine, Movement disorder, Org 3770, Review*

Introduction

Adverse events or unintended pharmacologic effects that occur when a medication is administered are stressful situations for patients and, in some cases, can be a challenge for the physicians [1]. In this context, movement disorders (MDs) associated with drugs are even more difficult to describe or give a clear diagnosis because the clinical manifestations could overlap and provide a mixture of disorders in the same individuals, also every movement type can be induced by some drug or toxin. The most frequent causes of drug-induced MDs are dopamine receptor blocking drugs, including antipsychotics and antiemetics [2].

Mirtazapine (MTZ) is an atypical antidepressant, which first clinical studies started at the end of the 1980s [3]. In 1994, this medication was primarily approved for the management of major depressive disorder (MDD) in the Netherlands. About three years later, MTZ was approved by the Food and Drug Administration for the treatment of moderate-to-severe depression [4]. A recent systematic review comparing the efficacy of more than twenty different antidepressants revealed that MTZ is one of the most effective antidepressants when compared to other antidepressants. It also demonstrated a statistical advantage over current selective serotonin reuptake inhibitors (SSRIs) [5]. However, currently, guidelines such as the National Institute for Health and Care Excellence in the United Kingdom 2010 still recommended generic SSRIs as the first-line treatment for depression [6].

The mechanisms of action involved with MTZ are the antagonism of central presynaptic adrenergic (α2), histamine (H1), and serotonin (SER) (5-HT2A, 2C, and 3) receptors [Figure 1]. In addition, it has moderate antagonist effects on peripheral alpha-1 adrenergic and muscarinic receptors [7]. The interference in these receptors explains the several significant side effects related to MTZ. The adverse events that affect more than ten percent of users are drowsiness, weight gain, and xerostomia.

MTZ was only approved by the FDA for the treatment of MDD [8]. However, this drug is used off-label for the

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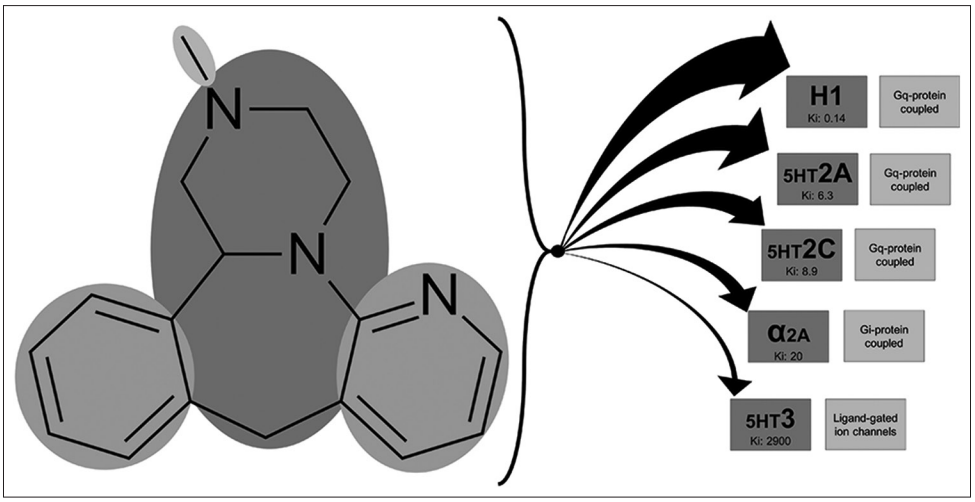

Figure 1: Skeletal formula and pharmacodynamic of mirtazapine. The size of the arrow is inversely proportionally to the Ki (smaller the value stronger is the drug binds to the site). Mirtazapine acts as antagonism of serotoninergic (5-HT2A, 5-HT2C, and 5-HT3), noradrenergic (α-2), and histaminergic (H1) receptors

management of posttraumatic stress disorder, hot flushes, insomnia, panic disorder, obsessive–compulsive disorder, generalized anxiety disorder, and headaches [4,8].

MDs are uncommonly related to MTZ. In the label of REMERON® (MTZ) tablets, in one of the clinical experiences in short-term United States control studies, nine individuals of more than four hundred taking MTZ had tremors, and this was the only MD found in more than one percent of the participants [9]. Moreover, other postmarketing studies done throughout the last decades including hundreds of individuals did not report any MTZ-induced movement [3]. A recent literature review of only the PubMed database from 1990 to June 2017 focused on hyperkinetic movements related to MTZ found twelve cases already reported, which were in descending order of frequency, akathisias (AKTs) (5), dystonia (DTN) (4), dyskinesias (DKNs) (2), and periodic limb MD (PLMD) (1). Their results conclude that these adverse effects were more common in older individuals, and the best treatment is the cessation of the medication [10]. The aim of this literature review is to evaluate the clinical epidemiological profile, pathological mechanisms, and management of MTZ-associated MDs.

Materials and methods

Search strategy

We searched six databases in an attempt to locate any and all existing reports on movement disorders secondary to mirtazapine published from 1990 to 2019 in electronic form. Excerpta Medica (Embase), Google Scholar, Latin American and Caribbean Health Sciences Literature (Lilacs), Medline, Scientific Electronic Library Online (Scielo), and ScienceDirect were searched. Search terms were "dystonia, restless legs syndrome, periodic limb movement disorder, akathisia, dyskinesia, tremor, stuttering, parkinsonism, tic, chorea, restlessness, ataxia, hyperkinetic, hypokinetic, bradykinesia, movement disorder, myoclonus, ballism." These terms were combined with "mirtazapine, Org 3770" [Supplementary Material 1].

Inclusion and exclusion criteria

Original articles, case reports, case series, letters to editors, bulletins, and poster presentations published from 1990 to 2019 were included in this review with no language restriction. The two authors independently screened the titles and abstracts of all papers found from the initial search. Disagreements between the authors were resolved through discussion.

Cases where the cause of MD was already known and either motor symptoms did not worsen or were not related to MTZ were excluded. Furthermore, cases that were not accessible by electronic methods including after a formal request to the authors (by email) were excluded. Cases that had more than one contributing factor to the MD were evaluated based on the Naranjo algorithm to estimate the probability of the event occurring.

Data extraction

A total of 3794 papers were found; 3444 were irrelevant and 298 were unrelated to the complication, duplicate, inaccessible electronically, or provided insufficient data [Figure 2]. Data abstraction was done. When provided, we extracted from the articles: authors' name, authors' department, year of publication, country of occurrence, number of patients affected, MTZ indication including off-label uses, time from first MTZ-dose until MD onset, time from MTZ withdrawal to symptoms improvement, patient's status at the last follow-up, and important findings of clinical history and management. The majority of the reports did not provide sufficient information about the neurological examination and the time from drug withdrawal to the improvement of the symptoms. The data were extracted by two independent authors, double-checked to ensure matching, and organized by whether the MD was a side effect of the MTZ use.

Statistical analysis

Categorical variables were represented as proportions; continuous variables were represented as mean, standard deviations (SDs), median, and range.

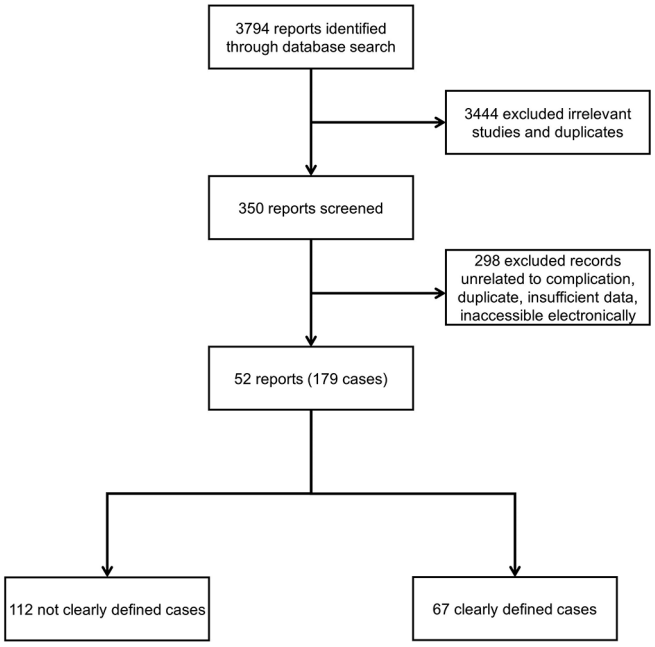

Figure 2: Flowchart of the screening process

Definitions

The clinical characteristics and definitions of the MDs such as DTN, restless legs syndrome (RLS), PLMD, AKT, DKN, tremor, parkinsonism, tic, chorea, ballism, and myoclonus were obtained from the reference Jankovic and Tolosa [11]. The clinical diagnosis for psychiatric disorders was obtained from the diagnostic and statistical manual of mental disorders (DSM-5®) [12]. The Naranjo algorithm was used for determining the likelihood of whether an adverse drug reaction was actually due to the drug rather than the result of other factors [13]. In the cases where the non-English literature was beyond the authors' proficiency (English, Portuguese, Spanish, Italian, French, and German) and the English abstract did not provide enough data, such as Japanese, Korean, Chinese, Russian, and Dutch, Google Translate service was used [14].

Results

For 1990 and 2019, a total of 52 reports containing 179 individuals that developed a MD associated with MTZ were identified from 20 different countries [Table 1] [10,15-65]. 103 individuals were from European countries, 49 Asian, 17 Australian, 8 North American, and 2 South American. Figure 3 shows the number of reports associated with MDs and MTZ over time. The MDs associated with MTZ encountered were 6 DTNs (isolated axial, isolated cervical, and axial + cervical), 69 RLS (induced and worsening RLS symptoms), 9 PLMD, 10 AKT, 3 DKN (chorea and choreoathetosis), 35 tremors (action and resting), 2 parkinsonism, 1 tic (complex motor facial without vocalization), 4 rapid eye movement sleep behavior disorders, and others not clearly identified cases such as 18 restlessness, 15 hyperkinesis, and 1 extrapyramidal symptoms.

The mean and median age was 57 (SD: 15.16) and 58 years (age range: 17–85). The female was the predominant sex in 60% (33/55) of the individuals. The most common

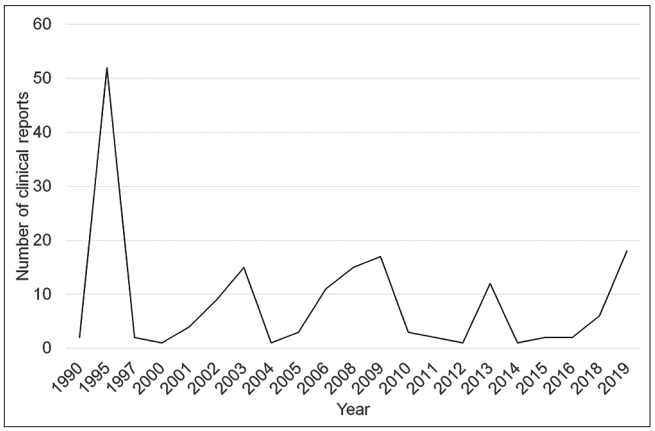

Figure 3: Graphic showing the number of clinical reports of mirtazapine-associated movement disorder from 1990 to 2019

indication of MTZ was MDD in 51% (21/41) of the cases, followed by MDD + insomnia (12), insomnia alone (3), hot flushes (1), major depressive episode (1), major depressive episode + insomnia (1), MDD + panic attacks (1), and mild depression + insomnia (1). The mean and median MTZ dose, when the MD occurred, was 24.68 (SD: 14.41) and 15 mg (MTZ dose range, 7.5–60). There were: 21 individuals with 15 mg of MTZ when the MD occurred, 19 with 30 mg, 7 with 7.5 mg, 4 with 45 mg, and 4 with 60 mg.

The mean and median time from MTZ start and the abnormal movement onset was 7.54 (SD: 15.53) and 2 days. The MD occurred within a week of the MTZ start in 78% (35/45) of the patients. The correlation between MTZ dose and the time from the drug start to the MD onset demonstrated a moderate linear correlation 0.367 when outliers were excluded.

Only two individuals did not have a complete recovery after the management. The time from drug withdrawal and the improvement of symptoms was specifically reported by 23 cases. In 19 cases, the recovery occurred within one week of the management.

In 82% (45/55) of the individuals, the management was the withdrawal of the offending drug. Other options were more commonly attempted on the MTZ-induced RLS, in which the management involved the inclusion of a new drug (clonazepam, ropinirole, pramipexole, or gabapentin) to improve the symptoms. In the AKT group, other choices to alleviate restlessness were attempted such as starting concurrent propranolol needed-basis, and as using every three days MTZ. By the way, in one individual with DKN, MTZ was not discontinued, and the symptoms improved over time.

Discussion

General

An important topic to discuss is the few numbers of clinical reports already reported in the literature of MTZ-induced MD. In this context, we believe that probably only were reported moderate to severe cases; on the other hand, those mild cases were only addressed by drug withdrawal without a report to the literature [66]. Some findings supporting this assumption are a large number of reports with thousands of cases about MTZ

Table 1: Clinical reports presenting with mirtazapine-associated movement disorder from 1990 to 2019

Reference	Country/year	Number of cases	Age/sex	MTZ				Follow-up	Important CH and CM
				Indication	Dose (mg)	MD onset	MD recovery		
DTN									
Lu *et al*.	USA/2002	1	63/male	MDD	15	9 days	4 days	CR	CH: Upper limbs DTN with myoclonic movements. CM: MTZ withdrawal
Van den Bosch *et al*.	Belgium/2006	1	79/female	ISI	30	1 day	2.5 days	CR	CH: The previous diagnosis of Alzheimer's dementia; developed isolated cervical DTN. CM: MTZ withdrawal
Guerrero *et al*.	Spain/2013	1	61/female	MDD, ISI	15	1 day	3 days	CR	CH: Axial and cervical DTN. CM: MTZ replaced by venlafaxine
Yoon	Korea/2018	1	54/male	MDD, panic disorder	15	7 days	21 days	CR	CH: Axial and cervical DTN. CM: MTZ withdrawal
Yamada *et al*.	Japan/2018	1	79/female	MDD	15	12 days	3 days	CR	CH: On the 3rd day, she developed parkinsonism; on the 12th day, an isolated axial DTN was noted. CM: MTZ withdrawal
Rissardo and Caprara	Brazil/2019	1	50/female	Hot flushes	15	4 days	5 days	CR	CH: Axial and cervical DTN. CM: MTZ withdrawal
RLS									
Markkula *et al*.	Finland/1997	2	55/female	MDD, ISI	30	5 weeks	<7 days, <7 days	CR	CM: MTZ withdrawal. After 1 week, MTZ-rechallenge and symptoms reoccurred. MTZ replaced by FXT
			26/male	MDD, ISI	30	6 weeks	NS	CR	CH: Previous moclobemide-induced ISI and fluvoxamine-induced AKT. CM: MTZ withdrawal
Bonin *et al*.	France/2000	1	33/male	MDD	15	7 days	7 days	CR	CM: MTZ replaced by fluvoxamine, and symptoms improve
Bahk *et al*.	Korea/2001	1	56/female	MDD	15	4 days	4 days	CR	CM: Clonazepam was added, which aggravated symptoms; MTZ replaced by paroxetine, symptoms total recovery
Agargun *et al*.	Turkey/2002	1	45/male	MDE, ISI	15-30	<7 days	NA	CR	CM: Clonazepam was added with full recovery
Teive *et al*.	Brazil/2002	1	78/female	MDD, ISI	30	NA	NA	NA	CH: Previous history of RLS; MTZ caused a worsening of RLS-symptoms. CM: MTZ was withdrawal; pramipexole started and the symptoms improved
Pae *et al*. No 1	Paet *et al*. describe the case by Bahk *et al*. in 2001. He adds that seven months later MTZ was rechallenge and the patient did not develop RLS symptoms								
Pae *et al*. No 2	Korea/2004	1	58/female	MDD	15-30	NA	NA	CR	CM: MTZ replaced by tianeptine and clonazepam; MDD recurred; MTZ-rechallenge without new RLS-symptoms
Kim *et al*.	Korea/2005	2	71/female	MDD, ISI	7.5	1 days	1 days	CR	CM: Brotizolam was started and maintained; no new RLS-symptoms
			58/female	MDD, ISI	7.5	1 day	1 days	CR	CM: Benzodiazepines were started and maintained without RLS-symptoms improve. MTZ was replaced by citalopram

Contd...

Table 1: Contd...

Reference	Country/year	Number of cases	Age/sex	MTZ				Follow-up	Important CH and CM
				Indication	Dose (mg)	MD onset	MD recovery		
Chang *et al*.	Taiwan/2006	1	32/male	MDE	30-60	8 days	3 days	CR	CH: He used domperidone previous, during, and after MTZ-use. CM: Clonazepam added no relief; MTZ replaced by cirzodone, and symptoms improved
Prospero-Garcia *et al*.	Mexico/2006	3	63/female	MDD	15	NA	2 days	CR	CM: MTZ withdrawal
			50/female	MDD	15	NA	2 days	CR	The 3 patients described belong to a clinical trial that the patients were treated with FXT, and after two weeks were randomly assigned for in addition to FXT receive MTZ or lorazepam. 5 patients used the combination MTZ+FXT, 3 of them developed RLS-symptoms
			41/male	MDD	15	NA	2 days	CR	
Kim *et al*.	Korea/2008	14	63/female	NS	7.5-60	1 day	NS	NA	CH: Previous diagnosis of RLS, which worsened after MTZ. CM: MTZ replaced by paroxetine
			45/male		7.5-60	1 day		NA	CH: Previous diagnosis of RLS, which worsened after MTZ. CM: MTZ replaced by trazodone
			43/female		7.5-60	1 day		NA	CH: Previous diagnosis of RLS, which worsened after MTZ. CM: MTZ replaced by bupropion
			59/male		7.5-60	1 day		NA	CH: Previous diagnosis of RLS, which worsened after MTZ. CM: GBP was started; the RLS-symptoms improved
			65/female		7.5-60	1 day		CR	CM: Ropinirole was started; RLS-symptoms improved
			71/female		7.5-60	1 day		CR	CM: MTZ replaced by trazodone. After a period, NS, the patient had a recurrence of the RLS-symptoms
			58/female		7.5-60	1 day		CR	CM: MTZ replaced by citalopram
			58/female		7.5-60	1 day		CR	CM: MTZ replaced by citalopram
			55/female		7.5-60	1 day		CR	CM: MTZ withdrawal
			67/female		7.5-60	3 days		CR	CM: MTZ replaced by trazodone
			80/male		7.5-60	3 days		CR	CM: MTZ replaced by bupropion
			65/male		7.5-60	3 days		CR	CM: MTZ replaced by bupropion
			71/male		7.5-60	10 days		CR	CM: MTZ withdrawal
			61/male		7.5-60	90 days		CR	CM: MTZ replaced by bupropion
Park *et al*.	Korea/2009	1	64/female	MDD	15-45	7 days	28 days	CR	CH: Pregabalin was added to MTZ; RLS-symptoms started. CM: MTZ replaced by bupropion with symptoms improve

Contd...

Table 1: Contd...

Reference	Country/year	Number of cases	Age/sex	MTZ				Follow-up	Important CH and CM
				Indication	Dose (mg)	MD onset	MD recovery		
Chopra *et al*.	USA/2011	1	85/male	Mild depression, ISI	15	NA	NA	CR	CH: RLS in use of ropinirole. MTZ worsened RLS-symptoms. CM: Ropinirole dose increased and he had hallucinations. Ropinirole and MTZ discontinued, low-dose GBP initiated, and the symptoms improved
Makiguchi *et al*.	Japan/2015	1	80/female	MDD	7.5-45	NA	NA	CR	CM: Pramipexole was added, and RLS symptoms resolved
Solmaz *et al*. No 2	Turkey/2016	1	56/female	ISI	15	4 days	NS	CR	CM: MTZ replaced by zopiclone
Yagli *et al*.	Turkey/2019	1	58/female	MDD, ISI	15	NS	NS	CR	CM: MTZ withdrawal
Patel *et al*.	India/2019	1	62/male	MDD	15	3.5 months	Days, NS	CR	CM: Pramipexole was added, and RLS symptoms resolved
PLMD									
Mattoo *et al*.	India/2012	1	28/male	ISI	15	1 days	NS	CR	CH: opioid detoxication. CM: MTZ withdrawal
AKT									
Lee *et al*.	Korea/2001	3	48/female	MDD, ISI	30-60	7 days	NS	CR	CM: Lorazepam was started, the symptoms little improve, MTZ was stopped and Trazodone dose was increased
			60/female	MDD, ISI	30	1 days	1 days	CR	CM: MTZ was withdrawal and symptoms recovery, after 5 days, MTZ rechallenge and symptoms return, MTZ replaced by nefazodone and symptoms recovery
			68/male	MDD	15-30	4 days	2 days	CR	CM: He had to worsen of symptoms with increase MTZ-dose; MTZ withdrawal with symptoms recovery, after NS time MTZ-rechallenge and the symptoms returned, MTZ was withdrawal
Girishchandra *et al*.	Australia/2002	2	73/female	MDD	15-30	1 days	1 days	CR	CM: MTZ replaced by fluvoxamine, the symptoms recovered. After 3-weeks, MTZ 30 mg rechallenge, the symptoms return, the drug was reduced and she had relief of the symptoms
			52/male	MDD	30	1 days	NA	CR, after clonazepam maintenance	CM: Clonazepam single-dose, he recovery; in the next day, symptoms return, new clonazepam dose; After, MTZ was maintained and clonazepam was started daily
Gulsun and Doruk	Turkey/2008	1	38/male	MDD, ISI	30	1 days	1 days	CR	CM: Diazepam IV was started and the symptoms improve. MTZ was replaced by citalopram

Contd...

Table 1: Contd...

Reference	Country/year	Number of cases	Age/sex	MTZ				Follow-up	Important CH and CM
				Indication	Dose (mg)	MD onset	MD recovery		
Ozyildirim *et al.*	Turkey/2009	1	43/female	MDD	15	1 year	NA	No	CM: She takes every three days the medication, and had AKT-symptoms on every dose for 8-10 h, but with two days asymptomatic
Markoula *et al.*	Greece/2010	1	72/female	MDD	30	20 years	First time 2 days	CR	CM: MTZ withdrawal, clonazepam started, and AKT-symptoms improvement. MTZ-rechallenge the symptoms returned after single-dose. MTZ replaced by amitriptyline. The AKT-symptoms improved and clonazepam was gradually discontinued
Raveendranathan and Swaminath	India/2015	1	42/female	MDD	15	1 days	NS, but was days	CR	CM: MTZ replaced by escitalopram
Koller	USA/2019	1	30/male	MDD	7.5-15	12 days	NA	CR	CH: multiple substance use disorder; He skipped some MTZ-doses and did not develop AKT-symptoms. CM: Benztropine did not improve AKT-symptoms, and was withdrawn. Propranolol improved AKT-symptoms and was continued as-needed basis
DKN									
Konitsiotis *et al.*	Greece/2005	1	63/male	MDD	30	1 days	NA	CR	CH: Chorea type DKN. CM: MTZ was continued and the abnormal movements were throughout the days decreasing in frequency and magnitude until the patient not developed any movement symptom
Balaz and Rektor	Czechia/2010	1	76/female	MDD	15	1 month	2 months	Good improve	CH: Choreoathetosis DKN. CM: Tiapride was started with mild improve RLS-symptoms. MTZ withdrawal.
Hutchins *et al.*	USA/2019	1	51/female	MDD	15-30	1 days	1 days	CR	CH: Previous history of RLS and orofacial DKN s induced by risperidone and olanzapine. CM: MTZ was withdrawal. After 1 month, MTZ rechallenge; she developed DKN. The MTZ-dose was increased and she did not develop new symptoms
Tremor									
Uvais *et al.*	India/2019	1	60/female	MDD, ISI	7.5	2 days	1 week	CR	CH: AKT and parkinsonism. CM: MTZ withdrawal and lorazepam started
TICS									
Liu *et al.*	Taiwan/2014	1	17/male	MDD, ISI	30	1 days	1 days	CR	CH: Complex facial motor tic without vocalization. CM: MTZ replaced by escitalopram

Contd...

Table 1: Contd...

Reference	Country/year	Number of cases	Age/sex	MTZ				Follow-up	Important CH and CM
				Indication	Dose (mg)	MD onset	MD recovery		
Not clearly defined cases									
Ruig *et al.*	Netherlands/1990	2	RLS	A double-blinded, placebo-controlled study that evaluates human sleep in 6 healthy subjects using 30 mg MTZ. None have PLMD-symptoms, but 2 subjects complained of" funny feelings in the leg"					
Montgomery	UK 1995	18 34	Restlessness Tremor	Review the clinical trials performed in Europe and the United States demonstrating MTZ safety					
Onofrj *et al.*	Italy/2002	4	REM sleep behavior disorder	19 individuals with L-dopa-responsive parkinsonism treated with MTZ for depression. 4 of them developed REM sleep behavior disorder. In 2, hallucinations and confusion were observed					
ADRAC	Australia/2003	15	Hyperkinesis	Number of reports to Australian Adverse Drug Reactions (ADRAC) Bulletin with MTZ from 2001 to October 2003					
Brown *et al.*	USA/2005	NA	RLS	A retrospective study of 200 patients taking antidepressants for ISI and RLS. MTZ was one of the medications associated, but NS data					
Freynhagen *et al.*	Germany/2006	3	RLS	594 individuals with MTZ. 37 developed side effects; 3 (0.5%) of these were MD and characterized as RLS					
Walinder *et al.*	Sweden/2006	3	RLS	192 individuals with MTZ for 12 months. 46 developed side effects; 3 (2%) of these were MD and characterized as RLS					
Rottach *et al.*	Germany/2009	15	RLS	53 individuals received MTZ. The study defined low-dose as 15 mg, which was in 5 patients. 15 MTZ-associated MD s, 12 developed and 3 had worsening of RLS-symptoms. The median days from drug start to RLS-symptoms was 2.5 days (range 1-23 days)					
Madhusoodanan *et al.*	USA/2010	1	EPS	A review that found 1 patient with EPS associated with MTZ, but they did not describe or give a reference for the study					
Bondon-Guitton *et al.*	France/2011	1	Parkinsonism	Review of notifications of DIP in a French regional pharmacovigilance center from 1993 to 2009. Of 155 reports 1 was due to MTZ. The individual clinical data is not provided					
Fulda *et al.*	Germany/2013	8 3	PLMD RLS	An open-labeled clinical trial that MTZ 30 mg was given to 12 healthy subjects and sleep was recorded. The mean age 22.25 (range 20-25), 8 developed PLMD and three of these had RLS-symptoms. The onset of PLMD-symptoms was since the first dose, but throughout the study, the symptoms improved. All had a CR after MTZ withdrawal					
Hong *et al.*	Korea/2016	1	Parkinsonism	Evaluated the role of functional neuroimaging for the dopamine transporter is used to distinguish DIP from subclinical Parkinson's disease. They report a 65-year-old male that had DIP after amitriptyline and MTZ use for 10 months					
Sung *et al.*	Korea/2016	NA	Parkinsonism	Role of nigrosome to differentiate DIP from Parkinson's disease. At least 1 individual developed DIP after MTZ, but they NS data					
Forcen *et al.*	USA/2017	NA	AKT	Drug-induced AKT in patients with cancer taking antipsychotics. At least 1 subject used MTZ, but they NS data					
Adabas and Uca	Turkey/2018	4	RLS	Assessed RLS-symptoms in 555 individuals using antidepressants in a Turkish population. 19 were in use of sertraline + MTZ (none patient developed RLS), 20 venlafaxine + MTZ (2 RLS), 18 paroxetine + MTZ (1 RLS), 7 escitalopram + MTZ (1 RLS)					
Hsu *et al.*	Taiwan/2019	NA	RLS	Use of antidepressants and risks of RLS in irritable bowel syndrome. At least one patient used MTZ, but they NS data					
Ocak *et al.*	Turkey/2019	6	RLS	The frequency of depression/anxiety disorder and antidepressants adverse effect in RLS. 12 individuals were using MTZ + SSRI (4 developed RLS) and 11 MTZ + SNRI (2 RLS). Patients with combined treatment (SSRI + MTZ) scored 4.7 times higher on the RLS scale					

AKT: Akathisia, CH: Clinical history, CM: Clinical management, CR: Complete recovery, DIP: Drug-induced parkinsonism, DTN: Dystonia, EPS: Extrapyramidal symptoms, GBP: Gabapentin, ISI: Insomnia, MD: Movement disorder, MDE: Major depressive episode, MDD: Major depressive disorder, MTZ: Mirtazapine, NA: Not applicable/not available, NS: Not specified SNRI: Serotonin and noradrenaline reuptake inhibitor, SSRI: Selective serotonin reuptake inhibitor, RLS: Restless legs syndrome, DKN: Dyskinesia, PLMD: Periodic limb movement disorder, FXT: Fluoxetine, ADRAC: Adverse Drug Reactions Advisory Committee

and MDs adverse effects on the FDA Adverse Event Reporting System [67]. In addition, more than eighty percent of the cases were diagnosed without the examination of a MD specialist. Thus, we presupposed that only the most severe cases with clear abnormal movements were published; also, it is worth mention that most cases did not clearly describe and lack significant features about the patients' neurological examination.

Herein, we would like to discuss some of the MDs in subtopics to give a better comprehension of the data. Figure 4 shows a resume of the hypothesized pathophysiological mechanisms that we proposed for the development of MDs following the use of MTZ.

Dystonia

In the cases related to DTN is observed the predominance of an elderly population, which could be explained by the reduced clearance of the drug that may increase the MTZ plasma levels and consequently the sensibility to the drug in this group of individuals [68]. In addition, most of the early studies about the efficacy of MTZ showed a higher percentage of side effects in the elderly population when compared to a younger population, even though only a small percentage of the total individuals belonged to this group [69]. Therefore, the initiation of MTZ in patients of sixty-five years or older should be at a low dose (7.5 mg or 15 mg) followed by a close follow-up.

When we analyzed the data found in Table 1 about all MDs, we can see that only in one patient MTZ-indication was not for a psychiatric disorder, which is important because it decreases the possibility of the MDs found in the literature be psychogenic disorders [65]. The most effective management was MTZ withdrawal.

The mechanism of DTN is poorly understood; as a result, we have many hypotheses in the literature [70]. Figure 4B shows the most common explanations for the MTZ-induced DTN found in the literature. One possible explanation for this association is an increased direct pathway stimulation by the frontal cortex in the substantia nigra compact due to the release of norepinephrine (NE) and SER from the 5HT2C antagonism in the raphe nucleus with cortical projections [71]; this is supported by studies showing frontal cortex hypermetabolism

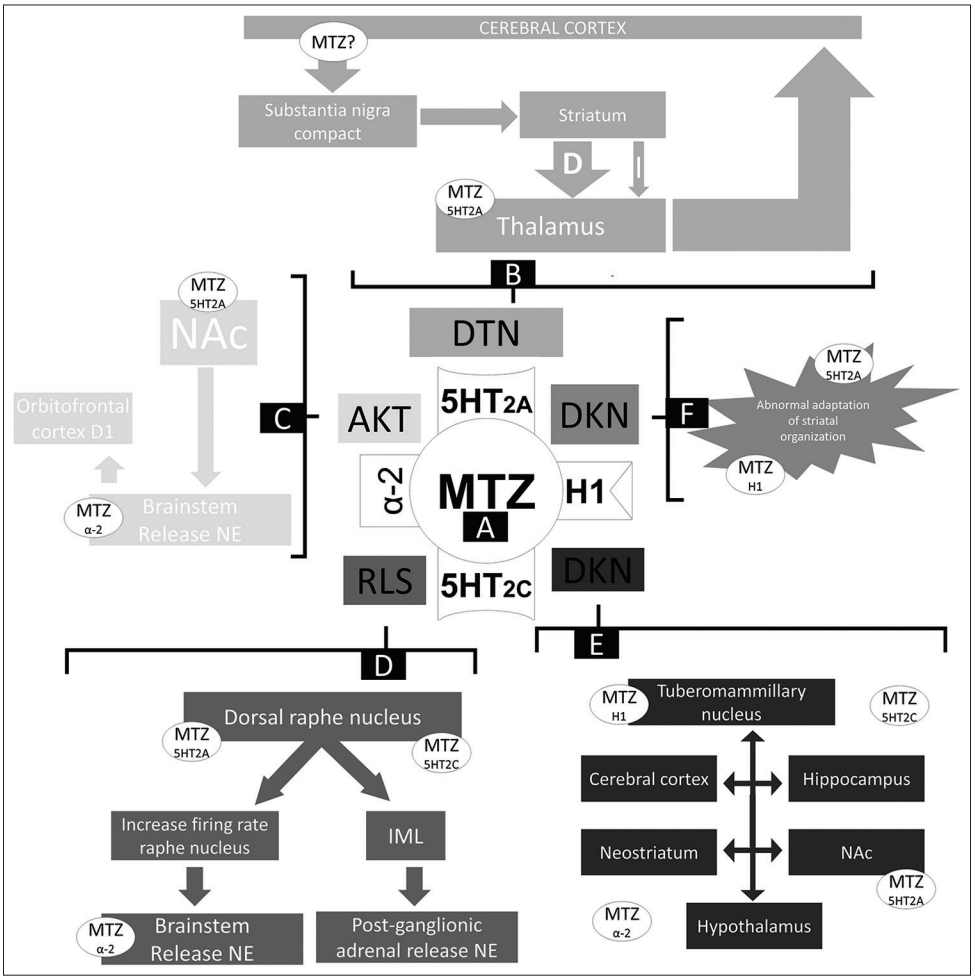

Figure 4: Schematic diagram showing the pathophysiological mechanism of mirtazapine-associated movement disorders. (A) Receptors that are significantly antagonized by mirtazapine, which include H1, 5HT2A, HT2C, and α-2. (B) Dystonia mechanism associated with 5HT2A; mirtazapine? Represents that probably mirtazapine has some indirect action in the pathway between the frontal cortex and substantia nigra compact. D: Direct pathway, I: Indirect pathway. (C) Akathisia mechanism associated with 5HT2A and α-2; NAc: Nucleus accumbens, NE: Norepinephrine. (D) Restless legs syndrome mechanism associated with 5HT2A, HT2C, and α-2; IML: Intermediolateral cell column. (E) Acute dyskinesia mechanism related to H1, 5HT2C, 5HT2A, and α-2. (F) Tardive dyskinesia associated with serotonin receptors and H1 antagonism that lead to abnormal adaptation of striatal organization

after MTZ [72]. Another theory could be the direct action in 5HT2A receptors in the thalamus, as was already found in animal models [73,74], leading to an increase of the thalamocortical drive by increasing direct pathway stimulation or decreasing the inhibitory projections to the thalamus [75]. Both hypotheses above have a common pathway that is the cortico–striato–pallido–thalamo–cortical loop, which was first characterized in DTN secondary to stroke [76,77].

Restless legs syndrome

RLS is probably the most underestimated of all abnormal movements secondary to MTZ. A prospective German study found that nine percent of patients receiving second-generation antidepressants had RLS-symptoms. In the study, 53 individuals were in use of MTZ, and more than twenty-five percent of these reported RLS-symptoms [40]. Thus, we believe that this study included individuals with mild symptoms of RLS rather than just moderate-severe reports like most of the data found in the literature. Furthermore, the use of specific questions during the appointments about RLS probably led the researches to increase the number of diagnoses. When evaluating depressed patients, another important feature that more commonly occurs with RLS than with other MDs is the mixture of the patients' symptoms, in which the RLS-symptoms go unnoticed or are ignored in the absence of a basic screening by the physician, and possibly occurs due to the various complaints from patients [78].

There are at least three hypotheses for the explanation of RLS [79]. The first hypothesis would be the prolonged use of dopamine antagonists, but we discard this theory because MTZ does not directly inhibit dopamine release. Another hypothesis is related to the central nervous system iron homeostasis, which was probably not the main mechanism responsible for the induced RLS because a long term alteration of the iron kinetic would be necessary to lead to abnormalities in the brain metabolism. The last hypothesis is an increase of SER in the brainstem [Figure 4D] [80]. In this context, the antagonism of 5HT2C and 5HT2A could lead to disinhibition of serotoninergic neurons, and consequently causing the release of SER [71,81]. The SER release can affect the intermediolateral column and nucleus and provoke postganglionic adrenal glands to release NE, which causes the discomfort sensation in the limbs [82]. Another possible pathway co-occurring is an increased firing rate of the raphe nucleus leading to NE release. Furthermore, NE release in the brainstem provokes insomnia, which is a common symptom reported by RLS patients [83,84].

It is worthy of mentioning that MTZ worsening RLS-symptoms of RLS symptoms is a common-sense association among MDs specialists. Hence, MTZ should be avoided in patients with a previous history of RLS [85]. In more than eighty percent of the MTZ-induced MDs, the management was drug withdrawal. However, in RLS, due to the lower severity of possible complications compared to other MDs, we may have more options depending on the situation. These choices include starting a new drug in association with MTZ to decrease the RLS symptoms, MTZ dose decrease, or even the rechallenge after a period of time. In this context, the MTZ rechallenge was attempted in two patients and was successful without the development of new symptoms.

Akathisia

The clinical description of the patients that developed AKT after MTZ use was the most comprehensible after the DTN group. However, sometimes, it was difficult to distinguish AKT patients from the RLS individuals due to overlap of the clinical manifestations of both disorders, what we will call AKT/RLS [86]. One possible explanation for this common association with MTZ is that this drug interferes in a variety of pathways at the same time due to similar Ki values; as a result, MTZ interacts with noradrenergic, serotoninergic, and histaminergic receptors at the same time.

An interesting fact in the AKT subgroup was that the majority of the individuals were middle-aged adults with a mean age of 48 years, which is almost ten years younger than the general findings associated with MTZ, and with Asian origin. These findings can support the hypothesis of a probable genetic predisposition in this subgroup of individuals.

The pathophysiological mechanism of MTZ-induced AKT is based on psychopharmacological studies with substance use disorder, mainly with addict users that had drug-seeking behavior [Figure 4C] [87]. It was already shown in rat models that 5HT2A antagonism leads to a decrease of dopamine in the surroundings of the nucleus accumbens, which signs by projections to the brainstem for release NE [87,88]. This neurotransmitter promotes the release of dopamine in the orbitofrontal cortex, leading to D1 hyperactivation and inducing AKT symptoms [88,89]. Furthermore, in the same context, MTZ antagonist effects on the central presynaptic alpha-2 antagonists cause an increased release of SER and NE in the brainstem reinforcing the process [7].

This MD was the only to reappear in all individuals that the drug was reintroduced. Thus, the best management in these situations should be the MTZ withdrawal without rechallenge. Also, if available, the prescription of a benzodiazepine for a short period of time due to possible faster recovery.

Dyskinesia

In the literature there is a lot of explanation about DKN secondary to medications, and many mechanisms were already proposed [90]. In Figure 4, we divided the DKN in Figure 4E, which represents the acute DKN, and Figure 4F, which represents the tardive DKN [91]. We explained the tardive DKN associated with MTZ based on findings with serotoninergic neurotransmission in rat models, where probably the effects on 5HT and MTZ metabolites lead to damage by inflammation and oxidative stress, which culminate in an abnormal adaptation of the striatal organization leading to direct pathway overactivation [92]. Otherwise, the acute DKN is probably more associated with antagonism H1 due to the time for the occurrence of the process described above; it is well known that antihistaminic medication can lead to DKN [93]. The histamine receptors are commonly found throughout the central nervous system, but an important structure with a lot of H1 is the tuberomammillary nucleus, which has many connections with the cerebral cortex, neostriatum, hypothalamus,

hippocampus, and nucleus accumbens [94]. In this way, we hypothesized that in susceptible individuals, the disturbance by MTZ antagonism effect in the H1 receptor, mainly localized, in the tuberomammillary nucleus may play a central role in the pathophysiological mechanism of the acute DKN.

Tremor, tics, and other movement disorders

Four patients were assumed to have a diagnosis of parkinsonism in the use of MTZ; only two were clinically reported as having secondary parkinsonism. Nevertheless, Yamada *et al.* and Uvais *et al*. did not clearly describe the neurological examination, and they lack information about the characterization of bradykinesia [57,63]. Therefore, even though the diagnosis of parkinsonism in those cases is possible, we believe that a diagnosis of an exacerbation of physiological tremor, which can be explained by the increase of NE release in a situation such as stress and anxiety, is more probable more probable [95]. In this context, MTZ interference in the α2 receptor enhances the release of NE and SER in the central nervous system leading to tremors [96]. Or even another possible pathway correlated with the RLS/AKT mechanisms can be suspected. One supporting feature of this theory is the fact that the general description of the patients' symptoms [63]. Moreover, the PLMD may also be related in the same way as tremor and RLS/AKT overlap pathways [97].

Tics were only reported in one individual, and Liu *et al*. proposed that tics may result in a dopamine surge by the interaction between serotoninergic receptors and the dopaminergic system [49]. They include that the hyperadrenergic status by the MTZ antagonism in the alpha-2 receptor could contribute to the development of the tics.

Other movements not clearly defined in some reports include the description of restlessness and hyperkinesis that are general terms. We believe that these cases were referring AKT, but the data about the specific symptoms and physical examination of the patients were not provided by the studies [25]. In addition, Madhusoodanan *et al*. reviewed the literature and found one patient with extrapyramidal symptoms associated with MTZ, but they did not describe or give a reference for the study [42]. As is in the majority of the cases, the management in these conditions was the drug withdrawal and the follow-up had good outcomes with fast and full recovery.

Conclusion

MTZ is associated with RLS, tremors, AKT, PLMD, DTN, rapid eye movement sleep behavior disorders, DKN, parkinsonism, and tic. In the literature, the number of reports about MTZ-associated MD is probably of only moderate–severe cases with lacking data about mild conditions. However, in general, this drug is probably uncommonly related to abnormal movements. The management should be the MTZ withdrawal, except in RLS cases that other options are possible. In AKT, the MTZ should not be rechallenge, and if available, the prescription of a benzodiazepine may reduce recovery time. Further reports of MTZ-associated MDs need to focus on the times of MD onset and recovery, as well as the long follow-up of the patient. These data should be provided for a future assessment of the significance of these abnormal movements to predict the development of MDs such as Parkinson's disease.

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Conflicts of interest

There are no conflicts of interest.

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