Cinnarizine- and flunarizine-associated movement disorder: a literature review

Jamir Pitton Rissardo and Ana Leticia Fornari Caprara

Abstract

Introduction: Cinnarizine (CNZ) and flunarizine (FNZ) belong to the calcium channel blockers class of medication.

Main text: The aim of this literature review is to evaluate the clinical epidemiological profile, pathological mechanisms, and management of CNZ/FNZ-associated movement disorder (MD). Relevant reports in six databases were identified and assessed by two reviewers without language restriction. One hundred and seventeen reports containing 1920 individuals who developed a CNZ/FNZ-associated MD were identified. The MD encountered were 1251 parkinsonism, 23 dyskinesias, 11 akathisia, 16 dystonia, and 5 myoclonus, and in the group not clearly defined, 592 extrapyramidal symptoms, 19 tremors, 2 bradykinesia, and 1 myokymia. The predominant sex was female with a percentage of 72.69% (466/641). The mean age was 74.49 (SD, 7.88) years. The mean CNZ dose was 148.19 mg (SD, 42.51) and for the FNZ dose, 11.22 mg (5.39). The mean MD onset and recovery were 1.83 years (SD, 1.35) and 3.71 months (SD, 1.26). In the subgroup of subjects that had improvement of the symptoms, the complete recovery was achieved within 6 months of the drug withdrawal in almost all subjects (99%). The most common management was drug withdrawal. A complete recovery was observed in 93.77% of the patients (437/466).

Conclusions: CNZ/FNZ-associated MD was extensively reported in the literature. Parkinsonism was the most well described. Myoclonus (MCL) was the poorest described MD with missing data about the neurological examination and electrodiagnostic studies. The knowledge of this disorder probably can contribute to the understanding of the other drug-induced MDs.

Keywords: Cinnarizine, Flunarizine, Review, Movement disorder, Drug-induced

Key messages

1. PKN is the most common described MD secondary to CNZ/FNZ treatment.
2. CNZ/FNZ mechanism of action is the blockage of dopamine, histamine, serotonin, and intracellular calcium-calmodulin complex.
3. All MD can be explained by the dopaminergic hypothesis, except MCL that is probably associated with serotonin.
predecessor [5]. In animal studies, FNZ showed an efficacy of 2.5 to 15 times stronger than CNZ [6]. It was first marketed in Europe around the 1980s about 10 years after the release of CNZ [3]. Spain among the European countries was one of the first in which FNZ was available [6] and probably the country with the greatest number of CNZ/FNZ prescriptions; in 1985, approximately 5% of the Spanish population over sixty were on CNZ treatment [3].

CNZ/FNZ has been used for several conditions including central and peripheral vascular disorders and balance disorders. Migraine, Raynaud syndrome, Ménière’s disease, vertigo, and tinnitus are examples of common indications of these drugs. The mechanism of action of CNZ/FNZ is poorly understood (Fig. 2) [2, 6–11]. These medications were first described as calcium channel blockers with activity in the L/T-type channels [6], but more recent studies showed that the main action of CNZ/FNZ may not be inhibiting calcium entry into cells, but rather by an intracellular mechanism such as antagonism of calmodulin [2, 11]. It is worthy of mentioning that this mechanism is postulated to be effective for the treatment of vertigo [2]. Other theorized interactions of this drug include the blockage of H1 histamine, 5-HT2c serotonin, and D2 dopamine receptors [6, 10]. The serotonergic mechanism is still poorly understood, some studies showed an increase [7] and in others a decrease [10] of the serotonin concentration in the synaptic cleft [6]. Thereby, we believe that these contradictory results probably occurred because different parts of the brain were studied.

The side effects observed in the first clinical studies of this drug in more than 1% of the population were drowsiness, nausea, indigestion, weight gain, feeling tired, stomachache, vomiting, sweating, and skin rashes [6]. Other adverse events were only reported in the postmarketing experience [12]. Some patients showed symptoms similar to Parkinson’s disease such as bradykinesia and resting tremors [13]. Later, many reports of drug-induced parkinsonism and other abnormal movements were reported with CNZ/FNZ [13–15], which sometimes are difficult to diagnosis in the clinical practice due to preexisting neurological and psychiatric comorbidities. In this way, the aim of this literature review is to evaluate the clinical epidemiological profile, pathological mechanisms, and management of CNZ- and FNZ-associated movement disorders.

**Methods**

**Search strategy**

We searched six databases in an attempt to locate any and all existing reports on movement disorders (MD)
secondary to CNZ and FNZ published between 1980 and 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 "parkinsonism, dyskinesia, dystonia, stuttering, myoclonus, restless legs syndrome, akathisia, tremor, chorea, tics, restlessness, ataxia, ballism, hyperkinetic, hypokinetic, bradykinesia, movement disorder." These terms were combined with "cinnarizine, flunarizine" (Other 1 - Supplementary material).

**Inclusion and exclusion criteria**

Case reports, case series, original articles, letters to the editor, bulletins, and poster presentations published from 1980 to 2019 were included in this review with no language restriction. The 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 CNZ/FNZ were excluded. Also, cases that were not accessible by electronic methods including after a formal request to the authors of the study by email were excluded. Cases that had more than one factor contributing to the MD were evaluated based on the probability of the event occurrence based on the Naranjo algorithm.

**Data extraction**

For CNZ/FNZ, a total of 4032 papers were found; 3431 were irrelevant and 484 were unrelated to the complication, duplicate, inaccessible electronically, or provided insufficient data (Fig. 3). Data abstraction was done. When provided, we extracted author, department, year of publication, country of origin, number of patients affected, CNZ/FNZ indication including off-label uses,
time from first CNZ/FNZ dose till MD onset, time from CNZ/FNZ withdrawal to symptoms improvement, patient’s status at follow-up, and important findings of clinical history and management. The majority of the reports did not provide sufficient information about the times of MD onset and recovery. 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 CNZ/FNZ use.

**Statistical analysis**
Categorical variables were represented as proportions; continuous variables were represented as mean, standard deviation (SD), median, and range.

**Definitions**
The clinical characteristics and definitions of the MDs such as parkinsonism, tics, dyskinesia, dystonia, myoclonus, restless legs syndrome, akathisia, tremor, chorea, ataxia, and ballism were obtained from the reference Jankovic and Tolosa [16]. The clinical diagnosis for the psychiatric conditions was obtained from the diagnostic and statistical manual of mental disorders (DSM-5) [17]. 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 [18]. 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 [19].

**Results**
For the years 1980 and 2019, a total of 117 reports containing 1920 individuals who developed a movement disorder associated with CNZ/FNZ were identified from 27 countries (Table 1) [3–5, 12–15, 20–129]. The origin was Asian in 834, European 663, South America 415, and North America 8. Figure 4 shows the number of reports associated with movement disorders and CNZ/FNZ over time with important markers of the history of the CNZ/FNZ-induced parkinsonism [13, 15, 53, 73, 79, 87, 115, 130]. The movement disorders encountered
| Reference                  | Country/year | N  | Age | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management                                                                 |
|----------------------------|--------------|----|-----|-----|----------------|----------------|----------------------------------|---------------------------------|-----------|------------------------------------------------------------------------------------------------------------------|
| **Parkinsonism**           |              |    |     |     |                |                |                                  |                                 |           |                                                                                                                  |
| Mello-Souza                | Brazil 1984  | 5  | NA  | NA  | FNZ            | NA             | NA                               | NA                              | NA        | CH: PKN + orofacial DKN + severe AKT + moderate DPS. Even after 20 months of drug withdrawal, she was still with severe AKT. CM: Drug withdrawal |
| Martí-Masso et al.         | Spain 1985   | 11 | 65–83| NA  | CNZ            | 150            | 6–36 months                      | NA                              | NA        | CH: PKN + CNZ + DKN. CM: Drug withdrawal                                                                             |
| Chouza et al.              | Uruguay 1986 | 12 | 70  | F   | FNZ            | 10–20 mg       | 9 months                         | NA                              | No        | CH: PKN +FNZ + orofacial DKN + severe AKT + moderate DPS. Even after 20 months of drug withdrawal, she was still with severe AKT. CM: Drug withdrawal |
|                           |              |    |     |     |                |                |                                  |                                 |           |                                                                                                                  |
| D’Alessandro et al.        | Italy 1986   | 6  | 67  | F   | FNZ            | 10             | 6 months                         | CR                              |           | CH: PKN + mild DPS. CM: Drug withdrawal                                                                             |
|                           |              |    |     |     |                |                |                                  |                                 |           |                                                                                                                  |
|                           |              |    |     |     |                |                |                                  |                                 |           |                                                                                                                  |
| Laporte and Capella        | Spain 1986   | 14 | 78  | M   | CNZ            | NR             | 4.5 years                        | NR                              | NR        | CH: All had some tremor or bradykinesia; two individuals had to worsen PD. CM: Drug withdrawal                     |
|                           |              |    |     | F   | CNZ            | 45             | 5 days                           | NR                              | No        |                                                                                                                  |
|                           |              |    |     | F   | CNZ            | NR             | 14                               | NR                              | NR        |                                                                                                                  |
Table 1 Clinical reports of CNZ/FNZ-associated MD (Continued)

| Reference          | Country/year | N cases | Age   | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management |
|--------------------|--------------|---------|-------|-----|----------------|----------------|---------------------------------|---------------------------------|-----------|---------------------------------------------------|
| Meyboom et al.     | Netherlands 1986 | 1       | 68    | M   | FNZ            | 10             | NR                             | Several months                  | CR        | CH: PKN + AKT +mild DPS. CM: Drug withdrawal       |
| Marti-Masso et al. | Spain 1987   | 4       | 62.5 (mean) | NA  | CNZ            | 150            | 58 days                        | NR                              | NA        | CH: Randomized trial of CNZ in 10 patients with PD. After 1 month, 40% (4/10) had to withdraw from the study due to the worsening of bradykinesia and tremor |
| Michele et al.     | Italy 1987   | 10      | 61–77 | NA  | FNZ            | NA             | NA                             | NA                              | NA        | Discusses the range of symptoms of PKN +DPS associated with dosages of FNZ |
| Micheli et al.     | Argentina 1987 | 11      | 69    | M   | FNZ            | 10             | 1 month                        | 3 months                        | CR        | CM: Drug withdrawal                                |
|                    |              |         | 68    | F   | CNZ            | 225            | 4 years                        | 5 months                        | CR        | CM: Drug withdrawal                                |
|                    |              |         | 82    | F   | FNZ            | 11.5           | 1 year                         | 15 days                         | CR        | CM: Drug withdrawal                                |
|                    |              |         | 73    | F   | CNZ            | 150            | 30 days                        | 17 days                         | CR        | CM: Drug withdrawal                                |
|                    |              |         | 74    | F   | CNZ            | 150            | 4 years                        | 20 days                         | CR        | CM: Drug withdrawal                                |
|                    |              |         | 61    | F   | FNZ            | 11.5           | 3 months                       | 5 months                        | CR        | CM: Drug withdrawal                                |
|                    |              |         | 71    | F   | FNZ            | 10             | 3 months                       | 1 month                         | CR        | CM: Drug withdrawal                                |
|                    |              |         | 73    | F   | CNZ            | 225            | 3 months                       | 3 months                        | CR        | CM: Drug withdrawal                                |
|                    |              |         | 74    | M   | FNZ+CNZ        | 10 + 150       | 7 months                       | 1 month                         | CR        | CH: PKN +DPS. CM: Drug withdrawal                  |
|                    |              |         | 82    | F   | FNZ            | 10             | 7 months                       | 24 days                         | CR        | CM: Drug withdrawal                                |
|                    |              |         | 67    | F   | FNZ            | 10             | 16 months                      | 6 months                        | CR        | CH: PKN +DPS. CM: Drug withdrawal                  |
| di Rosa et al.     | Italy 1987   | 42      | Elderly | NA  | FNZ            | NR             | Months                        | 12 weeks                        | NA        | CM: Drug withdrawal                                |
| Bakchine et al.    | France 1988  | 1       | 68    | F   | FNZ            | 10             | 10 weeks                       | 3 months                        | CR        | CH: PKN +AKT +orofacial DKN +DPS. CM: Drug withdrawal |
| Benvenuti et al.   | Italy 1988   | 27      | 74 (mean) | 19F | FNZ +   | 10             | 14 months (mean)               | < 6 months (96%)                | CR        | CM: Drug withdrawal                                |
| Capella et al.     | Spain 1988   | 39      | 78 (mean) | 24F | CNZ            | 156            | 14.67                          | < 6 months                      | CR        | CH: 3 patients were taking                         |
| Reference          | Country/ year | N cases | Age (mean) | Sex | Drug Suspected | Drug dose (mg) | Time from drug-start to symptoms (mean) | Time from withdrawal to recovery (90%) | Follow-up | Important clinical history and clinical management |
|--------------------|---------------|---------|------------|-----|----------------|---------------|-----------------------------------------|----------------------------------------|-----------|-------------------------------------------------|
| Lugaresi et al.    | Italy 1988    | 10      | 72 M       | FNZ | 10             | 40 months     | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 56 F       | FNZ | 10             | 5 months      | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 63 F       | FNZ | 10             | Some months   | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 52 F       | FNZ | 10             | 5 months      | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 72 M       | FNZ | 10             | Some months   | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 63 F       | FNZ | 10             | 5 months      | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 61 F       | FNZ | 10             | 8 months      | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 70 M       | FNZ | 5              | 6 months      | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 73 F       | FNZ | 5              | 9 months      | NR                                      | NR                                    | CM: Drug withdrawal |
|                    |               |         | 93 M       | FNZ | 10             | 4 months      | NR                                      | NR                                    | CM: Drug withdrawal |
| Moretti and Lucantoni | Italy 1988 | 24      | 71.1       | FNZ | 10             | 4.2 months    | < 4 months (50%)                        | NA                                    | CH: 10 individuals had PKN +DPS |
| Fontanari          | Brazil 1989   | 8       | 62 F       | FNZ | 10             | 6 months      | 3 months                                | CR                                    | CM: Drug withdrawal |
|                    |               |         | 65 F       | FNZ | 10             | 5 months      | 5 months                                | CR                                    | CM: Drug withdrawal |
|                    |               |         | 68 F       | FNZ | 10             | 3 months      | 4 months                                | CR                                    | CM: Drug withdrawal |
|                    |               |         | 62 F       | FNZ | 10             | 24 months     | NR                                      | NR                                    | CH: PKN +orofacial DKN. CM: drug withdrawal |
|                    |               |         | 63 F       | FNZ | 10             | 18 months     | 3 months                                | CR                                    | CM: Drug withdrawal |
|                    |               |         | 55 F       | FNZ | 10             | 4 months      | NR                                      | CR                                    | CM: Drug withdrawal |
|                    |               |         | 60 F       | FNZ | 10             | 3 months      | 6 months                                | CR                                    | CM: Drug withdrawal |
|                    |               |         | 63 F       | FNZ | 10             | 6 months      | 6 months                                | CR                                    | CM: Drug withdrawal |
| Kuzuhara et al.    | Japan 1989    | 31      | Adult      | FNZ | 10             | 6.1 months   | < 6 months (90%)                        | CR                                    | CH: Attempts with levodopa, anticholinergic drugs, and bromocriptine had been ineffective until FNZ withdrawal. 16 individuals had PKN+DPS and 5 PKN+AKT |
| Mangone et al.     | Argentina 1989| 21      | 68.5       | FNZ/CNR | 16 F + 5 M     | 15.7 months  | 2.6 months                            | CR                                    | CM: Drug withdrawal |
|                    |               |         | 2          | FNZ/CNR | 2 F           | NR          | NA                                    | NA                                    | CH: Worsening of PD symptoms |
| Micheli et al.     | Argentina 1989| 81      | 69.7       | FNZ/31CNZ/8CNZ+FNZ | 13.4/154.4 (mean) | 32.1/14.1 days (mean) | 80.5/105 days (mean) | CR | CH: 46 individuals had PKN +DPS. CM: Drug withdrawal |
| Mukai et al.       | Japan 1989    | 1       | Adult      | FNZ | NA             | NA          | NA                                    | NA                                    | CH: Showed slightly decreased |
### Table 1 Clinical reports of CNZ/FNZ-associated MD (Continued)

| Reference | Country/year | N cases | Age | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management |
|-----------|--------------|---------|-----|-----|---------------|----------------|-------------------------------|-------------------------------|-----------|---------------------------------------------------|
| Sa and Heinisch | Brazil 1989 | 19 | 75 | M | FNZ | 20 | 10 months | 30 days | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic and levodopa without success |
| 62 | F | FNZ | 20 | 2 months | 4 months | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic and levodopa without success |
| 71 | M | FNZ | 20 | 9 months | 30 days | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic and levodopa without success |
| 76 | F | FNZ | 10 | 2 months | 60 days | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic without success |
| 72 | F | FNZ | 10 | 1 year | 6 months | CR | CM: Previous of FNZ withdrawal was attempted levodopa without success |
| 65 | F | FNZ | 10 | 8 months | 4 months | CR | CH: PKN +DPS |
| 37 | F | FNZ | 20 | 8 months | 4 months | CR | CH: PKN +DPS |
| 67 | F | FNZ | 10 | 7 months | 3 months | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic without success |
| 64 | F | FNZ | 10 | 5 months | 60 days | CR | CH: PKN +DPS. CM: Previous of FNZ withdrawal was attempted anticholinergic and imipramine without success |
| 54 | F | FNZ | 10 | 6 months | 3 months | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic and imipramine without success |
| 69 | F | FNZ | 10 | 1 year | 50 days | CR | CH: PKN +DPS |
| 47 | F | FNZ | 10 | 15 days | 7 days | CR | CH: PKN +DPS |
| 72 | F | FNZ | 10 | 11 months | 30 days | CR | CH: PKN +DPS |
| 72 | F | FNZ | 10 | NR | 60 days | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic and levodopa without success |
| 68 | F | FNZ | 10 | NR | 60 days | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic and levodopa without success |
| 76 | F | FNZ | 10 | 11 months | 10 months | CR | CM: Previous of FNZ withdrawal was attempted anticholinergic without success |
| 74 | F | FNZ | 40 | 5 months | 60 days | CR | CH: PKN +DPS. CM: Previous of FNZ withdrawal was attempted levodopa without success |
| NR | F | FNZ | 20 | 7 days | 20 days | CR | CH: PKN +DPS |
| 66 | F | FNZ | 40 | 3 months | 60 days | CR | CH: PKN +DPS. CM: Previous of FNZ withdrawal was signal intensity of the putamen on brain MRI |
| Reference                  | Country/ year | N cases | Age | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management |
|---------------------------|---------------|---------|-----|-----|----------------|----------------|----------------------------------|------------------------------------|-----------|--------------------------------------------------|
| Trevisol-Bittencourt      | Brazil 1990   | 1       | 72  | M   | FNZ            | 10             | 8 months                        | 30 days                            | CR        | DB: attempted imipramine without success           |
| Fontanari                 | Brazil 1990   | 1 Adult |     | F   | FNZ            | NR             | NR                              | NR                                 | No        | CH: Drug withdrawal and biperiden started         |
| Gimenez-Roldan and Mateo  | Spain 1991    | 24      | 70.6 (mean) | 15 F + 9 M | CNZ             | 181.3 (mean) 4.2 years (mean) | NR                              | NR                                 | NR        | CR: She had PKN due to FNZ; the drug was removed, and she started to developing choreoathetotic DKN. Anticholinergics and levodopa did not ameliorate the DKN symptoms |
| Garcia-Ruiz et al.        | Spain 1992    | 32      | 72.6 (mean) | 26 F + 6 M | FNZ/27CNZ/1FNZ+CNZ | 8.75/122.5 (mean) 15 months (mean) | NR                              | NR                                 | NR        | CH: Only 3 patients had a full recovery. 44% had PKN +DPS. Patients younger than 73 years recovered better than older individuals |
| Morgante et al.           | Italy 1992    | 4 Adult |     | NR  | FNZ            | NR             | NR                              | NR                                 | NR        | CH: Only 3 patients had a full recovery. 44% had PKN +DPS. Patients younger than 73 years recovered better than older individuals |
| Negrotti et al.           | Italy 1992    | 25 Adult |     | NR  | FNZ/CNZ        | NR             | NR                              | NR                                 | NR        | CH: In the CNZ/FNZ-induced PKN there was a positive family history for PD or essential tremor with a greater percentage than the general population |
| Amancio et al.            | Brazil 1993   | 1 Adult |     | NR  | FNZ            | NR             | NR                              | NR                                 | NR        | CH: Only 3 patients had a full recovery. 44% had PKN +DPS. Patients younger than 73 years recovered better than older individuals |
| Cunha et al.              | Brazil 1993   | 11      | 67  (mean) | 8 F + 3 M | FNZ/CNZ         | 20/150 (mean) 24 months (mean) 2 months (mean) | CR                              |                                     |                                     |
| Galhardo et al.           | Brazil 1993   | 1 Adult | 48  | F   | FNZ            | 10             | 3 months                        | 90 days                            | CR        | CM: FNZ withdrawal; methixene and levodopa started |
| Llau et al.               | France 1994   | 16      | 65  (mean) | 10 F + 6 M | FNZ/CNZ         | NR              | 5.76 months (mean)              | NA                                 | NA        |                                     |
| Anjaneyulu and Mohandas   | India 1995    | 2 NA    |     | NA  | FNZ            | NA             | NA                              | NA                                 | NA        |                                     |
| Baquero et al.            | Spain 1995    | 18      | 66  (mean) | NA  | FNZ/CNZ         | NA             | 1 year (mean)                  | NA                                 | NA        |                                     |
| Claps                     | Chile 1995    | > 1 NA  |     | NA  | FNZ            | NA             | NA                              | NA                                 | NA        |                                     |
| Handforth et al.          | USA 1995      | 1 37    |     | F   | FNZ            | 60             | NA                              | NA                                 | NA        |                                     |
| Biary et al.              | Arabia 1995   | 1 52    |     | M   | FNZ            | 10             | 18 months (mean)               | NR                                 | NR        |                                     |
| Jimenez-Jimenez et al.    | Spain 1996    | 30      | 70  (mean) | 24 F + 6 M | FNZ/CNZ         | NR              | 60.9 months (mean) 4.5 months (mean) | CR                                 |                                     |
| Lee and Lee               | Korea 1996    | 3 64.33 (mean) |     | 2 F + 1 M | FNZ            | 10             | 3 months (mean)               | 4 months                            | CR        | CH: 2 PKN +DPS; 1 only PKN. Only one had a full recovery; others needed to take levodopa after the event |
| Reference                  | Country/year | N cases | Age (mean) | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management |
|----------------------------|--------------|---------|------------|-----|----------------|----------------|-----------------------------------|----------------------------------|-----------|--------------------------------------------------|
| Martinez et al.            | Chile 1996   | > 1     | NA         | NA  | FNZ/CNZ        | NA             | NA                                | NA                               | NA        | CM: Drug withdrawal                                |
| Morgante et al.            | Italy 1996   | 4       | 74         | M   | FNZ            | 10             | NR                                | NR                               | CR        | CM: Drug withdrawal                                |
|                           |              |         | 72         | M   | FNZ            | 20             | NR                                | NR                               | CR        | CM: Drug withdrawal                                |
|                           |              |         | 93         | F   | FNZ            | 10             | NR                                | NR                               | No        | CM: Drug withdrawal                                |
|                           |              |         | 62         | M   | FNZ            | 10             | NR                                | NR                               | NR        | CM: Drug withdrawal                                |
| Negrotti and Calzetti      | Italy 1997   | 11      | 69.5       | F   | 8FNZ/3CNZ      | 10/150         | 7 months                          | NA                               | No        | CH: 6 orofacial DKN; 3 limb DKN. No recovery. CM: Drug withdrawal |
| Cardoso et al.             | Brazil 1998  | 20      | NR         | NR  | 8FNZ/12CNZ     | NR             | NR                                | NR                               | NR        | CH: Only 4 individuals had a full recovery. CM: Drug withdrawal |
| Errea-Abad et al.          | Spain 1998   | 19      | Elderly    | 14F + 5M | 6FNZ/29CNZ/9FNZ+CNZ | NR        | NR                                | NR                               | NR        | CH: Only PKN, CM: Drug withdrawal                  |
| Garcia-Ruiz et al.         | Spain 1998   | 36      | 71.7       | 3F + 6M | 13FNZ/69CNZ/5FNZ+CNZ | 33 months (mean) | 5 months (mean)                  | CR (90%)                          |           | CH: Only PKN, CM: Drug withdrawal                  |
| Marti-Masso and Poza       | Spain 1998   | 87      | 75         | NR  | 7 CNZ          | 45.8 months    | NR                                | NA                               | CH: PKN +orofacial DKN            |
| Orti-Pareja et al.         | Spain 1999   | 7       | 75.6       | 5F + 2M | 2 CNZ          | 7 CNZ          | 45.8 months                      | NR                               | NA        | CH: PKN +orofacial DKN                            |
|                           |              | 1       | 75.6       | F   | 1CNZ           | NR             | NA                                | NA                               | CH: PKN +DTN                       |
|                           |              | 3       | 75.6       | 3F  | 3CNZ           | NR             | NA                                | NA                               | CH: PKN +AKT                       |
|                           |              | 3       | 75.6       | 3F  | 3CNZ           | NR             | NA                                | NA                               | CH: Only PKN, CM: Drug withdrawal |
| Stucchi-Portocarrero et al.| Peru 1999    | 1       | 25         | F   | CNZ            | NA             | 11 days                           | NA                               | NA        | CH: PKN +AKT +DPS, CM: Drug withdrawal; benzodiazepines, propranolol, and orphenadrine were started |
| Zamora and Argote          | Colombia 1999| 9       | 65         | F   | FNZ            | 10             | 4 years                           | NA                               | CH: Possible interaction with verapamil |
|                           |              | 77      | F           | FNZ | 10             | 1 year         | NA                                | NA                               | CH: Possible interaction with verapamil |
|                           |              | 65      | M           | FNZ | 10             | 6 months       | NA                                | NA                               | CH: PKN +DPS                       |
|                           |              | 76      | M           | FNZ | 10             | 6 months       | NA                                | NA                               | CH: PKN +DPS                       |
|                           |              | 51      | F           | FNZ | 10             | 3 months       | NA                                | NA                               | CH: PKN +DPS                       |
|                           |              | 51      | F           | FNZ | 10             | NR             | NA                                | NA                               | CH: PKN +DPS                       |
|                           |              | 57      | F           | CNZ | 75             | 3 years        | NA                                | NA                               | CH: PKN +DPS                       |
|                           |              | 68      | F           | FNZ | 10             | 3 years        | NA                                | NA                               | CH: PKN +DPS                       |
|                           |              | 62      | F           | FNZ | 10             | NR             | NA                                | NA                               | CH: Possible interaction with verapamil |
| Benito-Leon et al.         | Spain 2003   | 9       | NA         | NA  | 8CNZ/1FNZ      | NA             | NA                                | NA                               | NA        | CH: Possible interaction with verapamil            |
| Fabiani et al.             | Brazil 2004  | 4       | 61.75 (mean)| 2F | 2FNZ/2CNZ      | 11.2/72.1 (mean)| 16.5 months (mean)                | NR                               | CH: Only PKN, CM: Drug withdrawal |
|                           |              | 87      | F           | FNZ+CNZ | 10 + 75       | 16.5 months (mean) | NR | NR | CH: PKN +orofacial DKN +DPS |
| Reference | Country/Year | N Cases | Age (mean) | Sex | Suspected Drug | Drug Dose (mg) | Time from Drug-Start to Symptoms (months) | Time from Withdrawal to Recovery (months) | Follow-Up | Important Clinical History and Management |
|-----------|--------------|---------|------------|-----|----------------|---------------|------------------------------------------|------------------------------------------|-----------|---------------------------------------------|
| 1         | 76 F         | FNZ+CNZ | 10+75      | 16.5 months (mean) | NR | NR | CH: PKN +orofacial DKN |
| 5         | 66 (mean) 5F | 3CNZ/1FNZ/1CNZ+FNZ | 11.2/72.1 (mean) | 16.5 months (mean) | NR | NR | CH: PKN +DPS |
| Trevisol-Bittencourt et al. | Brazil 2005, 3 | 73.2 (mean) | F | CNZ/FNZ | NR | NR | CH: PKN +orofacial DKN |
| Barbosa et al. | Brazil 2006, 13 | 73.5 (mean) | NR | 7FNZ/6CNZ | NR | NR | CH: PKN +DPS |
| Louter and Tromp | Netherlands 2009 | Adult | NR | CNZ | NR | NR | CM: Drug withdrawal |
| Ma et al. | Korea 2009, 6 | 71.5 (mean) | NR | FNZ | 6.3 months (mean) | NR | NR |
| Mattos et al. | Brazil 2009, 1 | 74 | F | FNZ | 1 year | 10 months | CR | CH: Progressive supranuclear palsy like syndrome. CM: Drug withdrawal; levodopa, tolcapone, and memantine were started |
| Munhoz et al. | Brazil 2010 | 47 | 60.8 (mean) | NA | 34FNZ/13CNZ | NA | NA | NA |
| Masmoudi et al. | France 2011 | 80 | F | FNZ | 10 Months | NR | No | CH: PKN +orofacial DKN; possible interaction with trimetazidine; she did not recover the DKN |
| Arias | Colombia 2012 | 2 | 85 | F | FNZ | 20 | NR | 10 weeks | CR | CH: PKN +DPS. CM: Drug withdrawal |
| | | 28 | M | FNZ | 20 | 6 weeks | 10 weeks | CR | CH: PKN +DPS. CM: Drug withdrawal |
| Pioner et al. | Brazil 2012 | 1 | 56 | F | CNZ | 25 | NR | NR | CR | CM: Drug withdrawal |
| Kim et al. | Korea 2013 | 6 | 65 | F | FNZ | 10 | 12 months | NR | NR | CR | CM: Drug withdrawal |
| | | 62 | M | FNZ | 10 | 1 month | NR | NR | CH: PKN. CM: Drug withdrawal |
| | | 84 | F | FNZ | 10 | 3 months | NR | NR | CH: PKN. CM: Drug withdrawal |
| | | 70 | F | FNZ | 10 | 48 months | NR | NR | CH: PKN. CM: Drug withdrawal |
| | | 58 | F | FNZ | 10 | 1 month | NR | NR | CH: PKN +oromandibular DTN |
| | | 66 | F | FNZ | 10 | 3 months | NR | NR | CH: PKN. CM: Drug withdrawal |
| Gotardelo et al. | Brazil 2014 | 1 | 72 | F | FNZ | 10 Years 2 months | 2 months | CR | CM: Drug withdrawal; biperiden started |
| Miguel et al. | Portugal 2014 | 30 | 73.3 (mean) 22F+8M | FNZ/CNZ | NR | NR | CR (43%) | CH: 43% recovered only with withdrawal; the others needed a dopaminergic treatment for improving the symptoms |
| Chary and Krishnan | India 2016 | 1 | 37 | F | FNZ | 15 | 1 month 1 week | CR | CH: PKN +DPS. CM: Drug withdrawal; trihexyphenidyl started |
| Munhoz et al. | Brazil 2016 | 58 | 74.1 (mean) | NR | 38FNZ/20CNZ | 9.1/45 (mean) | 6 months | NR | NR |
| Nistico et al. | Italy 2016 | 2 | 64.19 (mean) | 2F | FNZ | NR | NR | NR |
Table 1 Clinical reports of CNZ/FNZ-associated MD (Continued)

| Reference            | Country/year | N cases | Age (mean) | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management |
|----------------------|--------------|---------|------------|-----|----------------|----------------|-----------------------------------|---------------------------------|-----------|---------------------------------------------------|
| Sung et al.          | Korea 2016   | 1       | 70.85      | 1F  | CNZ            | NR             | NR                               | NR                              | NR        | CH: Orofacial DKN, CM: Drug withdrawal            |
| Micheli et al.       | Argentina 1987 | 2       | 64         | F   | FNZ            | 10             | 3 months                         | 2 months                        | CR        | CH: Orofacial DKN (probably rabbit syndrome), CM: Drug withdrawal |
| Gabellini et al.     | Italy 1989   | 1       | 62         | F   | FNZ            | 10             | 1 year                           | 2 months                        | CR        | CH: Transient tongue tremor, CM: Drug withdrawal  |
| Mangone et al.       | Argentina 1989 | 6       | 68.5       | 5F + 1M | FNZ/CNR | NR             | NR                               | NR                              | 2 months  | CH: Orofacial DKN, CM: Drug withdrawal            |
|                      |              | 1       | 68.5       | 1F   | FNZ/CNR        | NR             | NR                               | NR                              | 2 months  | CH: Rabbit syndrome + AKT, CM: Drug withdrawal    |
| Micheli et al.       | Argentina 1989 | 9       | 74         | F   | FNZ            | 10             | 36 months                        | NA                              | No        | CH: Orofacial DKN + AKT, CM: Drug withdrawal     |
|                      |              | 59      | M          | CNZ | 225            | 36 months      | 2 weeks                          | CR                              |           | CH: Orofacial DKN + PKN + DPS, CM: Drug withdrawal |
|                      |              | 62      | F          | CNZ | 150            | 24 months      | 1 month                          | CR                              |           | CH: Orofacial DKN, CM: Drug withdrawal            |
|                      |              | 64      | F          | FNZ | 10             | 4 months       | 1 month                          | CR                              |           | CH: Orofacial DKN + PKN, CM: Drug withdrawal     |
|                      |              | 61      | F          | FNZ | 11.5           | 3 months       | 5 months                         | CR                              |           | CH: Orofacial DKN + AKT + PKN + DPS, CM: Drug withdrawal |
|                      |              | 70      | F          | FNZ+CNZ | 25/10 mg | 24 months      | NA                              | No                               |           | CH: Orofacial DKN + AKT, CM: Drug withdrawal     |
|                      |              | 68      | F          | FNZ | 10             | 48 months      | 5 months                         | CR                              |           | CH: Orofacial DKN + PKN + DPS, CM: Drug withdrawal |
|                      |              | 64      | F          | FNZ | 10             | 24 months      | NA                              | No                               |           | CH: Orofacial DKN + AKT + PKN, CM: Drug withdrawal |
|                      |              | 84      | M          | CNZ | 150            | 4 months       | NA                              | No                               |           | CH: Orofacial DKN + PKN, CM: Drug withdrawal     |
| Jimenez-Jimenez et al. | Spain 1996 | 2       | 70 (mean)  | 2F   | FNZ/CNR        | NR             | 60.9 months (mean)               | 4.5 months (mean)               | CR        | CH: Orofacial DKN, CM: Drug withdrawal            |
| Ortí-Pareja et al.   | Spain 1999   | 1       | 75.6       | F   | FNZ            | NA             | 45.8 months                      | NA                              | NA        |                                                   |
| Fabiani et al.       | Brazil 2004  | 1       | 72         | M   | FNZ            | 10             | 16.5 months (mean)               | NR                              | NR        |                                                   |
| Akathisia            | Micheli et al. Argentina 1987 | 1       | 54         | M   | CNZ            | 75             | 4 h                              | 1 day                           | CR        | CM: Drug withdrawal                               |
| Micheli et al.       | Argentina 1989 | 4       | 70         | F   | FNZ            | 30             | 48 months                        | 2 months                        | CR        | CH: AKT + Bruxism + PKN, CM: Drug withdrawal     |
|                      |              | 49      | F          | FNZ | 20             | 8 months       | 2 months                        | CR                              |           | CH: AKT + PKN + DPS, CM: Drug withdrawal          |
|                      |              | 66      | F          | FNZ | 10             | 18 months      | 2 months                        | CR                              |           | CH: AKT + PKN + DPS, CM: Drug withdrawal          |
|                      |              | 74      | M          | FNZ | 20             | 18             | 8 months                        | CR                              |           | CH: AKT + PKN + DPS, CM: Drug withdrawal          |
| Reference | Country/year | N cases | Age | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management |
|-----------|--------------|---------|-----|-----|----------------|----------------|----------------------------------|---------------------------------|----------|--------------------------------------------------|
| Garcia and Uriarte | Spain 1991 | 1 | Adult | NA | FNZ | NA | NA | NA | NA | |
| Anand and Thiagarajan | India 1993 | 1 | Adult | NA | FNZ | NA | NA | NA | NA | CH: AKT +DPS |
| Jimenez-Jimenez et al. | Spain 1996 | 2 | 70 (mean) | 2F | FNZ/CNR | NR | 60.9 months (mean) | 4.5 months (mean) | CR | |
| Micheli et al. | Argentina 1987 | 1 | 37 | M | FNZ+CNZ | 10 + 150 | 3 days | NA | NA | CH: Cervical DTN. CM: FNZ+CNZ was maintained |
| Mangone et al. | Argentina 1989 | 6 | 68.5 (mean) | 1F + 5M | FNZ/CNR | NR | NR | NR | CR | CH: Acute DTN that resolved after drug withdrawal |
| Micheli et al. | Argentina 1989 | 1 | 67 | F | FNZ+CNZ | 20 + 150 | 18 months | NA | No | CH: Blepharospasm + oromandibular DTN. CM: Drug withdrawal |
| Biary et al. | Arabia 1995 | 1 | 31 | F | FNZ | 10 | 3 months | NR | NR | CH: Cervical DTN |
| Jimenez-Jimenez et al. | Spain 1996 | 2 | 70 (mean) | 2F | FNZ/CNR | NR | 60.9 months (mean) | 4.5 months (mean) | CR | |
| Koukoulis et al. | Spain 1997 | 1 | 30 | F | FNZ | 10 | 2 months | 1 month | CR | CH: Blepharospasm. CM: Drug withdrawal |
| Fabiani et al. | Brazil 2004 | 1 | 61 | F | FNZ+CNZ | 11.2/72.1 (mean) | 16.5 months (mean) | NA | NA | |
| Alonso-Navarro and Jimenez-Jimenez | Spain 2006 | 1 | 53 | F | CNZ | 40 | 6 years | 1 year | CR | CH: Blepharospasm; she also had a history of DTN with thiethylperazine and sulpiride. CM: Drug withdrawal |
| Mathews et al. | India 2017 | 1 | 17 | F | CNZ | 25 | Single-dose | 1.5 days | CR | CH: Oromandibular and cervical DTN; possible interaction between CNZ and prochlorperazine. CM: Drug withdrawal; diphenhydramine started |
| Gallop et al. | UK 2019 | 1 | 10.5 (mean) | F | FNZ | 5 mg | NA | NA | NA | CH: Worsening of DTN; Sturge-Weber syndrome |
| Myoclonus | Turner et al. | Israel 2006 | 1 | 2.5 | F | CNZ | Overdose | NA | NA | NA | CH: Possible MCL (twitching in both hands) |
| Lopez-Castellanos et al. | El Salvador 2017 | 4 | 58 | M | FNZ+CNZ | NR | 1 week | 3 days | CR | CH: Multifocal MCL. CM: Drug withdrawal |
| | | | 66 | F | FNZ | NR | 20 years | 1 month | CR | |
| | | | 70 | F | CNZ | NR | 8 years | NA | No | CH: Multifocal MCL. CM: Drug withdrawal |
| | | | 69 | M | CNZ | NR | 3 years | 5 years | CR | |
| Cases not clearly defined | Marti-Masso Spain 1986 | > 1 | PKN | Case series showing that the worsening of PD is reversible with CNZ, but the MD may last several days or even weeks | |

**Table 1 Clinical reports of CNZ/FNZ-associated MD (Continued)**
Table 1 Clinical reports of CNZ/FNZ-associated MD (Continued)

| Reference                  | Country/ year | N cases | Age | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management |
|---------------------------|---------------|---------|-----|-----|----------------|----------------|-----------------------------------|--------------------------------|-----------|----------------------------------------------------|
| Giannaula et al.          | Argentina 1986 | 27      | EPS |     | Report of 27 individuals that developed PKN +DPS after CNZ/FNZ use |
| Amery                     | Belgium 1987  | > 1     | EPS |     | Reports about EPS following the use of FNZ |
| Baldarzi et al.           | Italy 1987    | 1       | Tremor | A young female presented with unilateral postural tremor after 10 mg FNZ for 2 months. Later, 4 months, she developed DPS. No signs of PKN were observed |
| Herskovits and Mangone    | Argentina 1987| > 1     | EPS |     | EPS following the use of CNZ/FNZ |
| Assmann et al.            | Netherlands 1988| > 1    | EPS |     | EPS following the use of FNZ |
| di Rosa                   | Italy 1988    | > 1     | EPS |     | EPS following the use of FNZ |
| Rostin                    | France 1988   | > 1     | EPS |     | Assessment of the efficacy of FNZ to the prophylactic treatment of migraine |
| Hefner and Fischer        | Germany 1989  | > 1     | PKN |     | Worsening of PD symptoms with FNZ |
| Jongerius and van Gool    | Netherlands 1989| > 1    | EPS |     | EPS following the use of FNZ |
| Mangone et al.            | Argentina 1989| 8      | Tremor | The symptoms started within 15 months of the beginning of the FNZ/CNZ and recovery in two months after drug withdrawal |
| Petri                     | Netherlands 1989| > 1    | EPS |     | EPS following the use of FNZ |
| Centozone et al.          | Italy 1990    | 1       | Tremor | Assessment of the efficacy of FNZ to the prophylactic treatment of migraine |
| Micheli et al.            | Argentina 1990| 2      | Bradykinesia | Assessment of the efficacy of FNZ to the management of Tourette’s syndrome |
| Senard et al.             | France 1990   | 6       | EPS |     | Report of 5F + 1M with 71.5 years (mean) who were n use of FNZ 11.66 mg when the EPS occurred. The EPS appeared after 7.0 (mean) months and disappeared after 2.2 (mean) months respectively |
| Wilder-Smith et al.       | Switzerland 1991| 1      | Tremor | Assessment of the efficacy of CNZ as an antiemetic for platin chemotherapy, possible interaction with metoclopramide and lorazepam |
| Curran and Lang           | Canada 1993   | 3       | Tremor | Assessment of the efficacy of FNZ in 10 patients with essential tremor. 3 individuals developed worsening of the symptoms |
| Beghi et al.              | Italy 1994    | > 1     | PKN |     | Pharmacoepidemiological study about the prevalence of PKN in Italy. Exposure to FNZ, neuroleptics was observed in 8 patients |
| Brucke et al.             | Austria 1995  | NA      | EPS |     | SPECT assessment in 26 individuals under FNZ/CNZ. It was observed that older age and long-term treatment are predisposing factors for EPS |
| Marti-Masso               | Spain 1996    | > 1     | PKN |     | Determine the prevalence of DIP in general neurology practice. During 1981–1988, the drug most often implicated was CNZ, though its relative impact decreased after |
| Vecchio et al.            | Italy 1996    | 3       | Tremor | Assessment of the efficacy of FNZ in 12 patients with essential tremor. 3 individuals had worsening of tremor, in the others nothing change |
| Verspeelt et al.          | Germany 1996  | 43      | EPS |     | Assessment of the efficacy of FNZ in vestibular vertigo and migraine |
| Orti-Pareja et al.        | Spain 1999    | 2       | Tremor | Reports of tremor following the use of CNZ (1) or FNZ (1) |
| Vazquez-Alen et al.       | Spain 2000    | > 1     | PKN |     | To determine demographic changes in an outpatient clinic in Spain about MD. It was observed a 40% decrease of the PKN during 1991–1998; the authors hypothesized that this occurred because of a reduction in prescriptions of CNZ/FNZ and flupentixol |
| Schillevoort et al.       | Netherlands 2002| > 1    | PKN |     | Data obtained from the PHARMO-database 1986–1998. CNZ/FNZ users were more likely to receive antiparkinsonian medication than non-users. Also, the use of antiparkinsonian medication was already elevated with CNZ/FNZ low doses and increased with increasing dose and duration of use |
were 1251 parkinsonism, 23 dyskinesias, 11 akathisia, 16 dystonia, and 5 myoclonus. In the group not clearly defined, 592 were extrapyramidal symptoms, 19 tremors, 2 bradykinesia, and 1 myokymia.

The resume data about CNZ- and FNZ-associated movement disorders is provided in Table 2. Herein, we will describe the general data of all clearly defined cases.

The predominant sex was female with a percentage of 72.69% (466/641). The mean and median age was 74.49 (SD, 7.88) and 71.1 years (age range, 2.5–93 years). The mean and median CNZ dose was 148.19 (SD, 42.51) and 154.4 mg (CNZ dose range, 5–225 mg) and for the FNZ 10 mg (FNZ dose range, 5–154.4 mg). The mean time from CNZ/FNZ start to the MD onset was 1.83 years (SD, 1.35). About 75% of the individual had abnormal movement within 3 years of the CNZ/FNZ treatment. The mean time from the CNZ/FNZ withdrawal until the MD recovery was 3.71 months.

### Table 1 Clinical reports of CNZ/FNZ-associated MD (Continued)

| Reference        | Country/Year | N cases | Age range (years) | Sex | Suspected drug | Drug dose (mg) | Time from drug-start to symptoms | Time from withdrawal to recovery | Follow-up | Important clinical history and clinical management |
|------------------|--------------|---------|-------------------|-----|----------------|----------------|-------------------------------|-------------------------------|-----------|---------------------------------------------------|
| Marti-Masso      | Spain 2005   | 2       | 71.1 years (2.5–93) | PKN | Retrospective study about the adverse effects of trimetazidine on motor functions. 4 patients were taking CNZ two developed PKN, and the other 2 did not have any adverse event |
| Foubert-Samier et al. | France 2012 | NA | 75 years (2.5–93) | PKN | Assessment of the long-term risk of developing PD after past exposure to neuroleptics and neuroleptic-like drugs. Concerning phenothiazines, the association with the risk of PD was mainly due to FNZ/CNZ (RR, 3.39; 95% CI, 1.20–9.58). Without FNZ/CNZ, the association was not statistically significant for phenothiazines (RR, 1.81; 95% CI, 0.71–4.64) |
| Lin et al.       | Taiwan 2016  | 280     | 75 years (2.5–93) | PKN | A population-based study assessing the risk for PKN in patients receiving FNZ/CNZ. The adjusted hazard ratio for PKN was 5.11 (CI = 3.758–6.967). Age, stroke, and diabetes mellitus were significant risk factors, but female sex and total doses of the studied drugs were not |
| Jhang et al.     | Taiwan 2017  | 497     | 75 years (2.5–93) | EPS | A population-based study assessing the risk for EPS in patients receiving FNZ/CNZ. The hazard ratio for EPS for FNZ CNZ were 8.03 (CI 6.55–9.84) and 3.41 (CI 2.50–4.63) |
| Yang et al.      | China 2017   | NA      | 75 years (2.5–93) | PKN | A population-based study assessing the risk of PKN in patients with DM. When FNZ is present, the hazard risk ratio is (1.21, 1.08–1.35) |
| Karsan et al.    | UK 2018      | 11      | 75 years (2.5–93) | EPS | Assessment of FNZ for the management of migraine. 11 individuals had possible EPS; 9 tremors and 2 with micrographia |
| Liang et al.     | Taiwan 2018  | NA      | 75 years (2.5–93) | PKN | Assessment of the risk of developing PKN after FNZ in patients with type 2 diabetes. The adjusted odds ratio was 2.75 (2.26–3.36) |
| Byun et al.      | Korea 2019   | NA      | 75 years (2.5–93) | PKN | Assessment of the prevalence of DIP and the utilization of offending drugs through an analysis of representative nationwide Korean data. From 2009 to 2015, it was observed a compound annual growth rate of 7.42% to FNZ |
| Jhang et al.     | Taiwan 2019  | NA      | 75 years (2.5–93) | PKN | Assessment of the risk of developing MD after FNZ. FNZ was associated with 240 PKN +48 hyperkineses. Higher exposure dose and duration, older age, history of essential tremor, and cardiovascular disease were associated with FNZ-associated MD |
| Kim et al.       | Korea 2019   | NA      | 75 years (2.5–93) | PKN | Assessment of the association between drug exposure and the risk of PKN using Korean population-based data. The odds ratio of FNZ when compared to those that never used it was 4.95 (2.71–9.03) |
| Lin et al.       | Taiwan 2019  | NA      | 75 years (2.5–93) | PKN | Assessment of the risk of developing PKN after FNZ in the database of Taiwan’s National Health Insurance Research Database. It is associated with older age, history of comorbidities, exposure to FNZ high-dose, and longer duration of exposure to FNZ |

Abbreviations: AKT akathisia, BD bipolar disorder, CH clinical history, CM clinical management, CNZ cinnarizine, CR complete recovery, DIP drug-induced parkinsonism, DKN dyskinesias, DPS depression, DTN dystonia, EPI epilepsy, EPS extrapyramidal symptoms, F female, FNZ flunarizine, M male, MCL myoclonus, MD movement disorder, NA not applicable/not available, NR not reported, PKN parkinsonism, PD Parkinson’s disease, PKN/FNZ flunarizine or cinnarizine, FNZ+CNZ flunarizine combined with cinnarizine
In the subgroup of subjects that had improvement of the symptoms, the complete recovery was achieved within 6 months of the drug withdrawal in almost all subjects (99%). Figure 5 shows a comparison between the percentage of patients developing a MD since the beginning of the drug and the percentage of patients recovering after drug withdrawal when outliers were removed.

The most common management was drug withdrawal. Other drugs prescribed after the CNZ/FNZ withdrawal included levodopa, anticholinergics (biperiden, trihexyphenidyl, methixene, orphenadrine), benzodiazepines, propranolol, diphenhydramine, and bromocriptine. In individuals that depression was observed, amitriptyline and imipramine were one of the medications started. A complete recovery was observed in 93.77% of the patients (437/466).

**Discussion**

**General**

Movement disorders (MD) associated with CNZ/FNZ were commonly reported in the literature. Historical facts probably have contributed to these findings such as the common sense about CNZ/FNZ be always in the list of the drugs that induced parkinsonism [131]; it was the second most common, only after antipsychotics, between the end of the 1980s and early 2000s [87]. Second, the wide number of CNZ/FNZ prescriptions all over the world because of the placebo drugs and the effect of “cerebral vasodilators” [3]. In this way, the well-known side effect and a large number of users’ mixture may explain some of the reports.

Based on the data available in Table 1, we can hypothetically illustrate a case. An elderly Asian female presented with symptoms of vestibular vertigo to her general practitioner. The physician started flunarizine 10 mg. In the long-term follow-up, within about 3 years of the beginning of FNZ, she complained of slow movements, stiffness, and resting tremor. She was diagnosed with drug-induced parkinsonism, and FNZ was withdrawn. Within less than 6 months, the patient had a full recovery.

The number of reports with FNZ was more than 60% of the overall data. Two characteristics of the metabolism of FNZ, when compared to CNZ, that can explain this are the long half-life, which is more than ten times the CNZ, and the accumulation in the central nervous system that is due to the fluorination; FNZ is much more lipophilic than CNZ [3, 6]. Moreover, we believe that another important aspect was the marketing issues with the general major availability of flunarizine all over the world [3].

The majority of the incidences of abnormal movements associated with CNZ/FNZ were not well described in the literature. Table 3 is a resume of the percentages of MD secondary to CNZ/FNZ; the data was extracted from clinical trials and other population-based studies [26, 34, 48, 49, 55, 70, 76, 77, 97, 115, 119, 123, 127, 129]. The incidences of CNZ/FNZ-induced abnormal movements, in general, vary throughout the literature, but the range is much smaller than other drugs with postmarketing evaluation such as valproic acid [132]; for example, extrapyramidal symptoms were found with the use of CNZ/FNZ in Verspeelt and
colleagues in 4.30% of individuals with migraine individuals, but in the vestibular vertigo subgroup it was 0.91%.

Herein, we would like to discuss some of the MD in subtopics to give a better comprehension of the data.

**Parkinsonism (PKN)**

**History (Fig. 4)**

The first report of FNZ-induced PKN was by the Brazilian neurologist De Melo-Souza during the IX Brazilian Congress of Neurology in 1984 [13]. His description of five elderly females who presented PKN and depression was a crucial observation for the knowledge of drug-induced MD [131]. Even though today, the number of cases has decreased and, in many countries, it has restricted prescriptions [2]; FNZ is a widely recognized drug as a cause of secondary abnormal movements and can be an example, as well as antipsychotics, for the MD. Nowadays, this association has been called De Melo e Souza’s syndrome by some authors [130].

**Incidence**

The incidence of PKN with CNZ/FNZ is scarce in the CNZ/FNZ label is that the occurrence is in 1 every 1000 users [6]; in the literature from data extraction of clinical trials, it is 0.07–6.52% (Table 3). It is noteworthy that the prescription of CNZ/FNZ should be avoided in PD. Martí-Massó and colleagues reported that 40% of PD

| Movement disorder | PKN | DKN | AKT | DTN | MCL | Others | General data |
|-------------------|-----|-----|-----|-----|-----|--------|--------------|
| Cases (%)         | 1251(65.15)| 23 (1.19)| 11 (0.57)| 16 (0.83)| 5 (0.26)| 614 (31.97)| 1920        |
| Continent (%)     | Asian| 332 (26.53)| 0 (0) | 1 (9.09)| 2 (12.5)| 1 (20) | 496 (81.10) |
|                   | European| 575 (45.96)| 4 (17.39)| 4 (36.36)| 5 (31.25)| 0 (0) | 75 (12.21)  |
|                   | North America| 1 (0.07)| 0 (0)| 0 (0)| 4 (80)| 0 (0)| 3 (0.48) |
|                   | South America| 343 (27.41)| 19 (82.60)| 6 (54.54)| 9 (56.25)| 0 (0)| 38 (6.18) |
| Sex (%)           | Female| 429 (34.29)| 19 (82.60)| 5 (45.45)| 10 (62.5)| 3 (60)| NA 466      |
|                   | Male| 161 (12.86)| 4 (17.40)| 2 (18.18)| 6 (37.5)| 2 (40)| 175         |
|                   | Unknown| 661 (52.83)| 0 (0)| 4 (36.36)| 0 (0)| 0 (0)| 1294        |
| Age (years)       | Range| 25–93| 59–84| 49–74| 10.5–70| 2.5–70| 2.5–93 (Md, 71.1) |
|                   | Mean| 75.63| 67.87| 64.71| 53.59| 53.1| 74.49 (SD, 7.88) |
| Number of reports with the drug (mean dose in mg) | CNZ | 347 (150.12)| 3 (175)| 1 (75)| 2 (325)| 3 | NA 356 (Mn, 148.19; SD, 42.51; Md, 154.4; Rg, 25–225) |
|                   | FNZ | 570 (11.19)| 10 (10.16)| 6 (20)| 3 (8.33)| 1 (NA)| 590 (Mn, 11.22; SD, 5.39; Md, 10; Rg, 5–60) |
|                   | FNZ +CNZ | 18 (12.08 + 133.06)| 1 (10 | 0| 3 (13.73 + 124.03)| 1 (NA)| 23 (Mn, 12.19 + 126.91; SD, 2.91 + 39.80; Rg, 8.75–20 + 25–154.4) |
|                   | Unknown | CNZ/FNZ | 316 | 9 | 14 | 8 | 0 | 951 |
| MD onset | Range | 2 days–5 years| 3 months–5 years| 1 day–5 years| 1 day–6 years| 1 week–20 years| 1 day–20 years (Md, 1.25) |
|                   | Mean (years) | 1.74 | 2.21| 2.54| 2.46| 7.75| Mn, 1.83 (SD, 1.35) |
| MD recovery | Range | 7 days–10 months| 2 weeks–5 months| 1 day–8 months| 1.5 days–1 year| 3 days–5 years| 1 day–5 years (Md, 3 months) |
|                   | Mean (months) | 3.61 | 2.45| 3.29| 4.41| 20.36| 3.71 (SD, 1.26) |
| Follow-up, % CR (number of reports) | 94.85% (406/428)| 66.66% (15/10)| 100% (7/10)| 91.66% (11/12)| 75% (3/4)| 93.77% (437/466) |

**Abbreviations:** AKT akathisia, CR complete recovery, DKN dyskinesia, DTN dystonia, MCL myoclonus, MD movement disorder, Mn median, Md mean, NA not available/not applicable, PKN parkinsonism, SD standard deviation, Rg range (minimum–maximum). In the “Others” subgroup are cases not specified about the movement disorder such as extrapyramidal symptoms, tremor, bradykinesia, and myokymia.
patients with short-term CNZ/FNZ use showed a severe worsening of the bradykinesia and gait [26].

Recent Asian population-based studies showed important features of the long-term CNZ/FNZ use and its complications [115, 119, 122, 124, 127–129]. Lin et al. [115] revealed that age, stroke, and diabetes mellitus are risk factors for the development of CNZ/FNZ-induced PKN. Kim et al. [128] showed that the odds ratio of the risk of developing PKN in FNZ users when compared to non-FNZ users is 4.95 (2.71–9.03). In another study, Lin et al. [129] revealed that a longer duration of exposure to FNZ and high FNZ doses are significantly associated with the occurrence of PKN.

**Epidemiology and diagnosis**

Among the CNZ/FNZ-induced MD, PKN was the most frequently described corresponding for more than half of the cases. The majority of the individuals affected were European, and mainly from Spain probably due to a large number of prescriptions and older European populations [3]. Three epidemiological findings of this

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**Table 3** Incidence of some abnormal movements in the literature

| MD       | Drug | Reference          | Year | NR | N   | Incidence | Studied disease     |
|----------|------|--------------------|------|----|-----|-----------|---------------------|
| PKN      | CNZ  | Martí-Masso et al. | 1987 | 4  | 10  | 40%       | Parkinson's disease |
| PKN      | FNZ  | Martinez-Lage      | 1988 | 1  | 1435| 0.07%     | Migraine            |
| Tremor   | FNZ  | Centozone et al.   | 1990 | 1  | 40  | 2.50%     | Migraine            |
| Bradykinesia | FNZ | Micheli et al.     | 1990 | 2  | 7   | 28.57%    | Tourette's syndrome |
| Tremor   | CNZ  | Wilder-Smith et al.| 1991 | 1  | 14  | 7.10%     | Emesis              |
| AKT      | CNZ  | Wilder-Smith et al.| 1991 | 1  | 14  | 7.10%     | Emesis              |
| PKN      | FNZ  | Handforth et al.   | 1995 | 1  | 16  | 6.25%     | Epilepsy            |
| EPS      | FNZ  | Biary et al.       | 1995 | 2  | 17  | 11.76%    | Essential tremor    |
| Tremor   | FNZ  | Vecchio et al.     | 1996 | 3  | 12  | 25%       | Essential tremor    |
| EPS      | FNZ  | Verspeelt et al.   | 1996 | 36 | 837 | 4.30%     | Migraine            |
| EPS      | FNZ  | Verspeelt et al.   | 1996 | 7  | 764 | 0.91%     | Vestibular vertigo  |
| PKN      | FNZ/CNZ | Lin et al.          | 2016 | 280| 9830| 2.90%     | Several             |
| EPS      | FNZ  | Jhang et al.*      | 2017 | -  | -   | 21.03%    | Several             |
| EPS      | CNZ  | Jhang et al.*      | 2017 | -  | -   | 10.30%    | Several             |
| Tremor   | FNZ  | Karsan et al.      | 2018 | 9  | 200 | 4.50%     | Migraine            |
| Micrographia | FNZ | Karsan et al.      | 2018 | 2  | 200 | 1%        | Migraine            |
| PKN      | FNZ  | Lin et al.*        | 2019 | -  | -   | 8.72%     | Migraine            |

**Abbreviations:** AKT akathisia, CNZ cinnarizine, EPS extrapyramidal symptoms, FNZ flunarizine, N number of individuals in the study, NR number of reports with the movement disorder, PKN parkinsonism

*Jhang et al. incidence rate (per 10,000 person-months); Lin et al. incidence rate (per 1000 person-years)
subgroup are comparable to the drug-induced PKN of the literature. First, the high incidence in females that is believed to be more susceptible [21], or we can presuppose that this was an occasional finding because females are related to a higher number of prescriptions. The results of Lin et al. that the female sex was not significantly associated with CNZ/FNZ treatment can support this hypothesis [115]. Second, the CNZ/FNZ-induced PKN occurred with higher CNZ/FNZ doses, which may be explained by higher doses leading to higher concentration in the central nervous system and a possible predisposition for the development of this MD [3, 6]. Third, an elderly population was more involved in this subgroup than in other abnormal movements that could be related to aging causing striatum abnormalities [9]; also, the possibility of FNZ/CNZ provoking PD cannot be ruled out.

The presentation in the majority of the cases was a symmetric akinetic-rigid syndrome, with resting and/or postural tremor; in almost half of the individuals, depression (mild, moderate, and severe) was described. Other commonly associated MD in descending order of frequency were akathisia, dyskinesia (orofacial, rabbit syndrome, choreoathetotic), and dystonia (oromandibular). Moreover, Mattos and colleagues reported a patient presenting with progressive supranuclear palsy like syndrome [102].

Sometimes, it can be hard to clearly distinguish between the CNZ/FNZ-induced MD and the idiopathic PD based only on clinical criteria. Thus, Teive et al. [131] selected some clinical tools from the studies of Negrotti and Calzetti [79] and Martí-Massó and Poza [73] to help on the diagnosis of this syndrome. Table 4 has the features by Teive et al. [131], and we propose a supporting feature that is the presence of another MD at the presentation; since an important percentage of the individuals is commonly affected by another disorder.

Pathophysiological mechanism

It is still not completely understood, but some authors believe that it is due to the decrease of dopaminergic neurotransmission [131]. In animal models, CNZ/FNZ decreased the concentration levels of dopamine probably due to tyrosine hydroxylase inhibition and dopaminergic neuron loss [8, 10]; also, the blockage of striatal dopaminergic receptors was observed [9]. We hypothesized that the calcium-calmodulin complex inhibition by CNZ/FNZ may be involved with the decrease of dopamine [11]; the involvement of only the release of dopamine without affecting its concentration or the noradrenaline/adrenaline concentration can support this assumption [10]. Furthermore, in the literature, studies have shown a decrease [10] and/or increase [7] in serotonin concentration with CNZ/FNZ; so, the serotoninergic hypothesis of PKN caused by a mechanism similar to that observed with serotonin reuptake inhibitors could have occurred in susceptible individuals [133].

Management

The most frequent management was the drug withdrawal and the rechallenge was not attempted in any of the cases. Some authors recommended the use of anticholinergics to accelerate the recovery and decrease the number of complications [42, 47]. A full recovery was observed in more than 90% of the cases.

Dyskinesia (DKN)

DKN was the second most commonly encountered MD secondary to CNZ/FNZ. More than 80% of the cases occurred in countries of South America. This can be explained by the great knowledge of this association leading to a possible more minute observation of the clinical findings [131]. The more frequent affected individuals were females 8 years younger than those developing PKN. Also, it was three times more common with FNZ than CNZ.

The presentation more frequently was orofacial. Rabbit syndrome was observed [15], which is an extrapyramidal adverse effect of antipsychotic medicines that perioral tremors occur at a rate of 4–5 Hz; we included in DKN, but there is controversy in the literature and some authors believed that is a separated disorder, which goes beyond the aim of this review. Gabellini and colleagues reported isolated tongue tremors, which was rarely observed in the cases reported in the literature [39].

The most common management was drug withdrawal. However, among the CNZ/FNZ-induced MD, DKN associated with CNZ/FNZ had the worst prognosis with a full recovery obtained in only 66% of the individuals.

One of the possible explanations for the occurrence of this MD is the dopaminergic hypothesis, which happens due to an abnormal adaptation of the striatal organization leading to overactivation of the direct pathway [134]. This hypothesis is plausible in the cases
reported and can be supported by the long onset time longer than the average. Moreover, the interaction of CNZ/FNZ with the histaminergic neurotransmission could have contributed to the development of this abnormal movement [6]. The H1 histamine receptors are commonly found in the tuberomammillary nucleus that has many connections with the cerebral cortex, neostriatum, hypothalamus, hippocampus, and nucleus accumbens [135]. Therefore, we believe that the long-term use of the medication can explain some of the cases, in a similar way to other antihistaminic drugs.

Dystonia (DTN)
DTN was observed in 16 individuals, and more than half was reported by South American authors. Some features of this subgroup that are commonly found in the drug-induced DTN literature include the prevalence of female sex predominance, affected younger population (compared to general data), low CNZ/FNZ doses associated with DTN, and short MD onset. The presentation in descending order of frequency was blepharospasm, oromandibular, and cervical; even worsening of a previous DTN was observed in a child with Sturge-Weber syndrome, when FNZ 5 mg was prescribed [126].

The dopaminergic hypothesis can explain the occurrence of CNZ/FNZ-induced DTN. The finding that antipsychotics that also interact with D2 dopamine receptors and are associated with DTN can support this assumption [134]. It has been suggested that the blockade of these receptors in the caudate, putamen, and globus pallidus is partly responsible for causing this abnormal movement [136]. Therefore, it is probably the disbalance of ratio dopamine-acetylcholine especially in the striatum that can produce these symptoms [9].

The most common management was drug withdrawal; in one case, diphenhydramine was started [121]. The complete recovery was noted in 91.66% of the patients.

Akathisia (AKT)
The majority of the reports associated with AKT occurred with higher FNZ doses that were almost twice the mean data. This MD most commonly occurred in the female sex from South America origin. Interestingly, AKT was the only MD associated with CNZ/FNZ that after the management 100% of the users had recovered, which we believed that probably occurred because the population affected was 10 years younger than the other MD. The most frequent management was drug withdrawal. Micheli and colleagues reported the first case of CNZ/FNZ-induced AKT; a middle-age male showed AKT symptoms after the first dose of CNZ 75 mg; the drug was withdrawn and the individual recovered in one day [28].

Since the CNZ/FNZ is involved with the dopaminergic system; this hypothesis can feasibly explain all extrapyramidal symptoms. Therefore, as well as PKN, DKN, and DTN, the D2 dopamine block is probably related to the occurrence of AKT [134].

Myoclonus (MCL)
This MD was rarely reported in the literature in association with CNZ/FNZ. Turner and colleagues reported a case of CNZ overdose in a child, she developed twitching in both hands [95]. However, they did not provide a clear description of the neurological examination neither of the electrodiagnostic studies. In another case series, Lopez-Castallanos and Lopez-Contreras reported four subjects in 2017 at the 1st Pan American Parkinson's Disease and Movement Disorders Congress [120]. The individuals were analyzed by a movement disorder specialist but no description of electromyography or electroencephalogram was done. The presentation was multifocal with or without a tremor. The management was drug withdrawal. Only one individual did not recover after 5 years of follow-up. Based on these two reports, we cannot conclude the source of MCL.

In the literature about drug-induced MCL, the most common hypothesis is associated with the serotoninergic neurotransmission. This abnormal movement was already reported with the increase and the decrease of serotonin concentration [137]. In this context, CNZ/FNZ was first believed to decrease the serotonin concentration, in the synaptic, by the induction of monoaminergic neuron damage probably because the higher number of reports with depressive symptoms in the clinical practice [10], but some studies have shown a contradictory increase of the serotonin that happened due to serotonin reuptake blockage and facilitation of its release [7]. We believed that these different results could have occurred due to different brain sites being studied. Therefore, the increase of this neurotransmitter may be related to MCL in susceptible individuals.

Conclusion
In sum, CNZ/FNZ-associated movement disorders were extensively reported in the literature probably due to important historical features. The most frequent and well-described MD was PKN. MCL was the poorest described MD with missing data about the neurological examination and electrodiagnostic studies. In descending order of frequency, the following MD related to CNZ/FNZ were encountered: PKN > DKN > DTN > AKT > MCL. Most of the CNZ/FNZ-induced MD can be explained by the dopaminergic hypothesis, except MCL that is probably associated with serotonin. We believe that the knowledge of the abnormal movements associated with CNZ/FNZ could significantly raise the awareness of the
potential motor side effects secondary to other commonly prescribed drugs. In this way, the continuum development of new drugs with fewer or less severe side effects is essential for the improvement of the quality of life, reduction of negative outcomes, and increase of patients’ adherence.

**Supplementary information**

Supplementary information accompanies this paper at https://doi.org/10.1186/s41983-020-00197-w.

**Additional file 1:** Other 1 – FreeText and MeSH search terms in the US National Library of Medicine

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**Authors’ contributions**

JPR and ALFC contributed equally to the research idea, data acquisition, data analysis, interpretation, and manuscript review. Both authors read and approved the final manuscript.

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**Availability of data and materials**

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