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Tremor and Other Hyperkinetic Movements

Reviews

Tardive Dyskinesia-like Syndrome Due to Drugs that do not Block Dopamine Receptors: Rare or Non-existent: Literature Review

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Abstract

Background: Although tardive dyskinesia (TD) is most commonly defined as a movement disorder caused by chronic exposure to dopamine-receptor-blocking drugs (DRBDs), it has also been thought to result from exposure to some non-DRBDs.

Methods: We critiqued many reviews making the association between non-DRBDs and a TD-like syndrome and almost all case reports. We checked whether cases met criteria for the diagnosis of TD-like syndrome and whether DRBDs had been excluded.

Results: We found that both tricyclic antidepressants and selective serotonin reuptake inhibitor antidepressants may unmask or exacerbate TD after prior exposure to or with concurrent use of DRBDs. We found support for its existence outside of this context to be extremely weak.

Discussion: There is little evidence that drugs other than DRBDs by themselves cause a TD syndrome; most reported cases appear to occur as a result of a "priming" effect induced by a DRBD, which is later unmasked.

Keywords: Tardive Dyskinesia, Non-dopamine receptor antagonists, Antidepressants, Antiepileptics, Anticholinergics, Antihistamine

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Introduction

The association between long-term exposure to DRBDs and persistent, usually irreversible, movement disorders is well accepted, but whether chronic exposure to drugs not known to block dopamine receptors can also cause a similar syndrome is unclear. We reviewed the reports making this association to determine if such an association is likely to exist.

There is no single consensus definition of tardive dyskinesia (TD). The definition has been revised within the discipline of psychiatry with each edition of the Diagnostic and Statistical Manual of Mental Disorders, the standard reference for the diagnosis of psychiatric disorders. The most recent edition, (DSM-V), published in 2013, defines TD as "involuntary athetoid or choreiform movements lasting at least a few weeks, developing in association with the use of a neuroleptic medication for at least a few months, and persisting beyond 4–8 weeks".[1] This is the most often used definition. Use of this definition would obviate the need for this paper; however, a syndrome with a similar phenomenology has been ascribed to non-dopamine receptor blocking drugs (DRBDs) and is considered to be a form of TD.[2–7] Cornett et al.[7] in their review used the DSM-V definition, but extended potential etiologic drugs to include non-DRBDs.

It is important to note that in the literature the term "TD" is used both as an umbrella term to include a variety of movement disorders associated with long term use of neuroleptics, including dystonia and akathisia, as well as a specific, oral–buccal–lingual choreo-athetoid movement disorder, typically seen after long-term DRBDs.[8] In this manuscript, we will use the term TD to include all the choreo-athetoid, stereotypic movements and limit this report to that subset of tardive syndromes, excluding other tardive syndromes such as akathisia, tics, and dystonia. The great majority of reports on non-DRBD-induced

TD pertain to choreo-athetoid movements; therefore, this is not a significant restriction. The second largest number of reports is on akathisia, which is a not uncommon acute side effect of selective serotonin reuptake inhibitors (SSRIs), and confounds our ability to distinguish an acute from a tardive syndrome. The other syndromes are much less commonly described in publications.

The difficulties in associating movement disorders with particular medications other than DRBDs include the rarity of the problem, the often unverifiable medical history, and the occurrence of similar movement disorders with no clear etiology in an untreated population.

In the early years after neuroleptics were introduced, the choreo-athetoid and stereotypical movements were recognized, but it was not clear whether they were associated with the treatment or the underlying diseases[9]. The concurrence of a variety of movement disorders with schizophrenia, in particular, and other mental illnesses had been recognized for many decades prior to the development of antipsychotic and antidepressant drugs, which confounded the interpretation of the newly developing movement disorder.[10,11] This was due to the reasons just listed, plus the current lack of diagnostic clarity. The recognition that TD was a diagnostic entity secondary to neuroleptics was due to the rapidly increasing number of cases identified as drug use increased, making the association undeniable, after early skepticism.

In evaluating the association between dyskinesias and the possibility of non-DRBD etiologies, the situation is quite similar to that of the early days of neuroleptic use. Isolated cases were reported and the association with particular drugs was suspected, but not provable. However, with neuroleptics, once the syndrome was identified it became clear that the association was robust. This is not the case with non-DRBDs. While many cases have been reported, the majority are not convincing. Their occurrence appears to be quite rare, making alternative explanations, such as inadequate history and non-diagnosed concurrent, but unrelated, primary neurological disorders, more likely. Finally, psychogenic (functional) movement disorders may be enriched in populations exposed to psychoactive drugs, and can be difficult to diagnose reliably. As early as 1992, Fishbain et al.[12] suggested the possibility that non-DRBD TD-like disorders likely unmasked or exacerbated underlying movement disorders, rather than caused them.

Two illustrative cases

Case 1

A 70-year-old male had prominent oral–buccal–lingual dyskinesias. He was nearly edentulous and had been on risperidone and quetiapine in recent years. He and his wife reported that his mouth movements had not changed since they had first appeared over 40 years ago, prior to losing any teeth or having taken any psychiatric medications. While this case appears to be a "classic" case of TD, exacerbated by the absence of teeth, the history does not support this diagnosis. Unfortunately, there is no way to check the history.

Case 2

A 79-year-old retired, female psychiatric registered nurse was evaluated for tremors and falls. She had a gait abnormality ascribed to vascular disease, although without a history or magnetic resonance imaging evidence of a stroke. She was found, coincidentally, to have classic TD signs of chewing movements and tongue writhing severe enough to cause tongue ulcers. She had been taking paroxetine for over 15 years, and tricyclic antidepressants (TCAs) prior. She had also taken prochlorperazine for only a few days at a time during her chemotherapy cycles for chronic lymphocytic leukemia. She had never been on other DRBDs. The movements postdated her use of prochlorperazine.

These two cases are our own and are similar to those in the literature ascribed to antidepressant medications. The first case might be a case of spontaneous oral facial dyskinesias,[13,14] which, if it occurred after exposure to an antidepressant, might have been considered another case, or our history is incomplete. The second case had only minimal exposure to a DRBD, and might have been included in most of the reviews discussed in detail below.

Methods

We used the definition of TD employed by a recent review,[7] even though old case reports relied on earlier DSM editions. Our review was not complete due to difficulty accessing old articles. We assessed whether cases were on concurrent DRBDs, had known exposure to DRBDs, had statements specifically excluding a history of DRBD use, the time of onset of the movement disorder with respect to the non-DRBD, and the duration of the movement once the DRBD was discontinued.

The authors reviewed most, but not all articles (see below), in PubMed and Web of Science under the search headings TD, movement disorders, extrapyramidal syndrome, and drugs either by class (antidepressants, SSRIs, TCA, anxiolytics, sedatives, hypnotics, anticonvulsants/anti-epileptics, antihistaminic, amphetamine, anticholinergic, stimulants) or individual names (phenytoin, fluoxetine, lithium, etc.). We reviewed over 300 articles that were reviews, small series, or case reports. These were difficult to review since they were old, and thus without abstracts on PubMed, often letters to the editor, and also without abstracts for quick review. Thus, the review was systematic and relatively, but not fully, comprehensive.

Results

The striking feature of most review articles is their failure to use defined criteria for TD in their citations or in their own cases that they added. In general, most reviews cited previous review articles that themselves cited cases, or other reviews, many of which cited cases that did not fit any current definition for a "TD-like" syndrome, that is, a new movement disorder that persisted for a defined period of time after the drug was withdrawn. All had dyskinesias, but most lasted for short periods of time, while on the offending drug, and resolved quickly when it was removed. Equally importantly, almost all reports included, with little or no discussion, cases with concurrent or prior exposure to

DRBDs. Few reports specifically stated that they had excluded a history of DRBD exposure, or performed an evaluation to exclude a primary cause for the movement disorder. The following evaluation of major reports reviewing the topic of TD and non-DRBDs provides some details.

Cornett et al.[7] cite four references for TD. In one,[15] the patient developed acute mandibular dystonia within 2 days of treatment with fluoxetine; dystonia improved soon after discontinuation. The second citation listed three cases, one of which had been on DRBDs.[16] Neither of the other two cases excluded a history of DRBDs. The third citation described one case of their own, which had prior DRBD exposure and mentioned nine other cases, of which one was on concomitant DRBDs and eight did not meet the criteria for a diagnosis of TD.[3] Clayton et al.[4] described one case of their own, which meets the criteria for inclusion here and 17 other cases,[17–28] all of which had prior DRBD exposure or did not meet criteria for TD. In sum, this paper lists 32 purported cases of TD induced by antidepressants of which a single case meets our criteria for non-DRBD-induced TD.

Leo's[5] report was a review with no new cases added. Eight citations were included for "TD-like" syndromes ascribed to SSRIs. All are included in other discussions within this paper.[3,12,29–34] Fishbain et al.[12] case qualifies under our criteria. None of the others meet the criteria for non-DRBD-induced TD either because of concurrent or past DRBD use[3,29–33] or failure to exclude a history of DRBD.[34] Yassa et al.[27] evaluated 50 patients hospitalized for depression and found three cases of "TD," one on amoxapine, a DRBD, and two on doxepin, but there was no mention of possible prior use of DRBD. Onset was abrupt with doxepin and resolved quickly when the drug was stopped. The two cases without clear DRBD exposure did not meet clinical criteria for TD.

A chapter in an e-textbook of neurology on TD cites three references in support of non-DRBDs causing TD.[2] One report describes a patient on concurrent DRBDs.[35] One undoubtedly had been on neuroleptics prior to receiving clozapine for longstanding psychosis, and thus had prior DRBD use,[36] although not explicitly stated. The third citation is a review paper, which described 12 cases, 10 of whom had DRBD exposure, an 11th with cerebellar disease, etiology unstated, and one without stated explicit exclusion of prior DRBD exposure.[37]

In a large review by Hawthorne and Caley,[6] 18 cases are cited, eight of whom were taking or had taken DRBDs.[38–45] An additional case was a 15-month-old child with stereotypies and repetitive movements prior to treatment and most others without an adequate description of previous drug therapy to exclude DRBDs. In only three cases was it clearly stated that no known DRBD exposure existed,[46–48] and the movements persisted for a few weeks after drug discontinuation in one case, and less than 4 months in another case.[46] One of the cases with no DRBD history,[47] however, had suffered Traumatic Brain Injury (TBI) requiring surgical evacuation of intraparenchymal hematomas. In five cases neuroleptic exposure was not commented upon[49] or the clinical picture was not compatible with the definition of TD.[49–52]

Lee and Nam[40] cited five reports of TD induced by SSRI and added a single case of their own. Their case had prior DRBD use. One report described two cases, neither of which meet the criteria for TD.[53] Another did meet the criteria but did not exclude DRBDs.[34] One excluded DRBD history and still met the criteria for TD but specifically doubted that the SSRI was causal (see quote above).[12] One report[54] had acute akathisia and no dyskinesias. Their fifth citation, which described three of their own cases, had one with prior DRBD use and two in which prior use was not excluded.[16]

In a review of SSRI-induced movement disorders, 12 cases of dyskinesia were noted in their database, 10 of whom had DRBD exposure and one had prior cerebellar dysfunction.[37] Whether the 12th specifically denied DRBD use is unstated. All were women. The paper also cited 34 "sertraline-induced dyskinesia" cases reported to Pfizer, of whom five were taking neuroleptics, two had a prior movement disorder, and no data were available for the others. Eli Lilly reported 76 cases related to fluoxetine, but no data for DRBD were included. This paper also added six other SSRI-associated cases, of which one[53] was not TD; the others are in reference citations.[16,30,34] Another similar review on SSRIs[5] reported cases on concomitant DRBDs or history of DRBD use;[3,30] non-TD cases;[3,29,31,33] failure to exclude a history of DRBDs;[34] an unknown number of dyskinesia cases included in a report of 15 cases with a variety of extrapyramidal disorders, of whom five were on concurrent DRBD, with no information about prior use of DRBD provided for the others.[32] One case,[12] noted above, did meet our criteria.

There is a single report of buspirone causing a TD-like syndrome in one patient. This patient had primary torticollis, then developed classic TD on a DRBD that worsened with buspirone,[55] and therefore does not meet criteria.

Fann et al.[18] cites reports of purported TCA-induced TD cases. Some were on concomitant DRBD;[19,27,28] some had prior use of DRBDs;[18,22] some did not meet clinical criteria for TD;[24,26,27] some did not specifically mention history of possible DRBDs or thought it partly due to primary brain disease.[17] The eleventh report,[17] which included one case of their own that meets our criteria for TD-like and no DRBD exposure, also referenced 17 others, who were all patients with DRBD use prior to onset.[4] Thus, there was one case meeting our criteria from 10 reports citing 31 purported cases.[17]

Another review[56] of purported SSRI-induced TD cases cited cases that were on DRBDs[30,32] or had taken DRBDs,[3,29,31,56] but also referred to four that did not have TD[23,53,56,57] and one case in which prior DRBD was not excluded;[34] there were five cases[17] in which DRBDs are not clearly excluded and in which the movements were thought due primarily to primary brain disorder. Thus, this paper cited a single case of SSRI-induced TD not clearly exposed to DRBDs.

A second review on TCA-induced TD reported one case with prior DRBD,[18] one with concurrent DRBD,[19] one case that did not exclude DRBD use,[57] and two cases that were not TD.[23,24] This paper also noted cases of dyskinesia reported to the Food and Drug Administration of adverse event reports, of which there were 89 cases. The authors estimated the incidence of any movement-disorder-related adverse event at less than one per 1,000 among SSRI users (no time period provided). This review also cited other reviews

previously discussed.[5,37] In one, five cases were reported, with problems as noted above.[17]

The proper documentation of TD criteria with drugs other than antidepressants is even less detailed, and the same limitations presented above, such as improper diagnosis, lack of differentiation between other hyperkinetic syndromes and TD, and incomplete documentation of associated drug use and drug exposure history, are frequently observed. For instance, Cornett et al. [7] cite anti-epileptic drugs (AEDs). In reality, one reference cited describes a link between tics and carbamazepine and lamotrigine. [58] The only other AED in their report is phenytoin. Dyskinesias associated with phenytoin in the report were acute or associated with other signs of phenytoin toxicity, [59–63] a well-known disorder unrelated to TD.

Other reports on dyskinesias and phenytoin share the same characteristics and were either acute, after therapy initiation, or drug increase, or present during episodes of intoxication.[64,65] Two cases of dyskinesias reported with gabapentin did not fulfill the criteria for TD.[66] Carbamazepine-induced dyskinesias were reported due to intoxication[67] or concomitant use of lithium.[68] Interestingly, one study found that co-administration of carbamazepine and a second-generation antipsychotic increased the risk of movement disorders.[69] In a study, 201 patients with epilepsy were evaluated by a movement disorders specialist for the presence of movement disorders. Postural tremor was the most common finding, observed in 89 patients, followed by parkinsonism in nine, dystonia in four, and tics in two. There were no reports of TD.[70]

Although retrospective in nature and performed in 1999, another study involving five movement disorders center identified 100 patients[64] who fulfilled the diagnosis of a tardive syndrome, of whom 72 had TD. Either AEDs, antihistamines, anticholinergics, or amphetamines were implicated as the causative agent in those cases.[71]

Reports of TD caused by antihistamines,[72–74] anticholinergics,[75–77] and amphetamines[78] suffer from the same shortcomings as described for those caused by antidepressants. In a report of two cases of orofacial dyskinesias and the use of antihistaminic decongestants, one case had been exposed to fluphenazine and the other to bultalbital and chlordiazepoxide.[72] Therefore, the latter case may not be DRBD-related. Clark et al.[73] described a case of head rolling, lip-licking, and athetoid tongue movements in a 74-year-old female using daily hydroxyzine for 7.5 months. The patient, however, had intermittently used phenothiazine for nausea previously and was also using doxepin. Lastly, a case of oromandibular dystonia in a 53 year old was attributed to daily use of cetirizine for 7 years. Discontinuation of the drug did not lead to improvement.[74] Although there is a clear temporal association, a causal relationship is hypothetical.

A few reports often used the term "dyskinesia," in isolation, without using the term TD.[3,79] However, review articles citing these reports frequently then classified the case report as a TD-like syndrome, which was based entirely on the phenomenology of the movements, and not the temporal relationship between the movements and the implicated drug, time of onset of the movements, or duration after stopping the presumed offending agent. The striking feature in most review articles is their failure to use defined criteria for TD before including their citations. In general, each review article cited previous review articles that included citations that generally did not fit any current definition for a "TS-like" syndrome, that is, a new movement disorder that persisted for a few weeks after the drug was withdrawn.[7] Equally important, almost all reports included, with little or no discussion, prior exposure to DRBDs, thus suggesting that the non-DRBD "unmasked" rather than caused the disorder. For example, Mander et al.[3] describe one case of their own, previously on DRBDs, and provide a review of other cases, but include eight cases of non-TD movement disorders plus one TD case taking high-dose metoclopramide. Thus, all their cases had priming with DRBDs.

Discussion

Reports on TD (see Table 1) in non-DRBDs are primarily isolated case reports and small series, (mostly one case, and none larger than five),

Table 1. **Reports of TD in non-DRBD in the literature**

Authors	No. of Reported Cases	Cases Meeting Criteria
Hawthorne and Caley[6]	18	0
Lee and Nam[40]	8	1
Gerber and Lynd[37]	46	0
Bharucha and Sethi[53]	9	0
Coulter and Pillans[32]	15	1
Leo[5]	8	1
Clayton et al.[4]	32	1
Cornett et al[7]	14	0

the vast majority of which had a history of either prior or concurrent use of DRBDs, a clinical syndrome that was not compatible with TD, usually resolving within days of drug discontinuation, or a history of prior use of DRBD was not excluded. Reviews usually cited previous reviews, which themselves included cases that did not meet the criteria for a diagnosis of TD. Only rare cases of TD ascribed to non-neuroleptics had complete evaluations for other causes of the movements; however, it is unlikely that many were actually caused by such a disorder.

Many of the reports include patients who had been exposed to neuroleptics, but not in recent times. There is no consensus criterion for how long a patient may be off a DRBD and develop a movement disorder that may be ascribed to the drug. One review stated that "exposure to DRBD within 1 year prior to the onset of the tardive syndrome to be causally related."[2] It is also unclear what it means to ascribe causality.[80] Our interpretation of the data is that DRBDs generally provide some sort of "priming" effect, which then, on rare occasion, with the addition of non-DRBD drugs, unmasks "latent" TD. Conversely, a very small subset of patients with a combination of certain genetic factors could potentially develop TD after exposure to non-DRBD drugs.[81,82]

In 1992 Fishabain et al.[12] noted, "The dyskinesia associated with antidepressants and also with fluoxetine appears to differ from that of neuroleptics. Antidepressants, including fluoxetine, may exacerbate rather than cause the pathophysiological process involved in the dyskinesia." It is possible that non-DRBDs really have extremely weak dopamine-receptor-blocking properties, below the level of current detection.

Conclusion

We believe, like Fishbain et al., [12] but now with several more cases for support, that non-DRBD psychoactive drugs of various types, most commonly SSRIs and TCAs, unmask or exacerbate a dyskinetic disorder due to DRBDs via mechanisms not currently understood. Our interpretation of the data suggests that antidepressants may increase the risk of clinically identifiable TD in patients who have taken DRBDs, even in the remote past. It also suggests that TD-like syndromes in patients never on DRBDs must be an extraordinarily rare event so that SSRIs, TCAs, and other non-DRBDs should not be considered causal until other explanations have been excluded.

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