Antipsychotic-Induced Tardive Movement Disorders: A Series of Twelve Cases

Duangjai Kasantikul MD*,
Buranee Kanchanatawan MD*
* Department of Psychiatry, Faculty of Medicine, Chulalongkorn University

Background: Prolonged use of antipsychotic drugs (AP) with or without sudden withdrawal as well as high dosage of AP (at least 3 months) may result in a variety of movement disorders such as classical tardive dyskinesia (tongue rolling, lip pouting, trunkal choreiform movements), tardive myoclonus (sudden, brief involuntary jerking), tardive dystonia (tongue protrusion, torticollis, scoliosis, jaw spasm, bruxism, abnormal trunkal posture, or “Pisa syndrome”, strong contraction of arm and leg). Patients with severe symptoms often suffer from body pain and fractures of bones due to frequent fallings. They are also accused of “faking” to call attention or they believe that the symptoms are signs of being “cursed or posses in”.

Objective: To report twelve patients of antipsychotic drug induced tardive movement disorders including tardive dystonia, tardive myoclonus, and tardive Parkinsonism. Patients were incorrectly diagnosed as epilepsy, conversion (pseudo seizure), or hypochondriasis.

Results: In the present series, there were eight men and four women with age ranging from 13 to 72 years. All patients had been taking both typical and atypical antipsychotic drugs for at least one year. Strong involuntary movement disorders, torticollis, scoliosis, body pain, difficulty in swallowing, and aphonia were observed. Most patients were thin and anemic. They responded well to diazepam, anticholinergic drug, clonazepam, lithium, and antidepressant while antipsychotic drugs were discontinued in most cases. Calcium salt and iron supplement appeared to be useful.

Conclusion: Physicians should be aware of these abnormal movement disorders induced by AP drugs to detect early and provide prompt treatment. AP drug should be used cautiously to prevent this iatrogenic effect particularly in high-risk patients.

Keywords: Antipsychotic drug, Tardive syndromes, Tardive dystonia, Tardive myoclonus, Tardive parkinsonism

Full text. e-Journal: http://www.medassocthai.org/journal

Prolonged use of either typical or atypical antipsychotic (AP) drugs may induce tardive movement disorders that often cause great distress and may become a permanent disability to patients[1-13]. There are several forms of tardive syndromes such as the classical tardive dyskinesia (TD), tardive dystonia (TDt), tardive Parkinsonism (TP), and tardive myoclonus (TM), etc[4,5,9]. It has been suggested that tardive syndromes may result from an imbalance between the cholinergic and dopaminergic system in the basal ganglia[4,5]. However, high serum homocysteine or Ca[2]

Correspondence to: Kasantikul D, Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
contraction (seizure-like) and can involve any part of the body. Most cases are mild; therefore, patients may not be aware and fail to report their symptoms to the clinician. In severe cases, patients may experience strong contractions of arm, leg, and shoulder. TP is not common and its clinical features include tremor at rest, stiff gait, bradykinesia, excessive salivation, and masked face.

Most patients with tardive syndromes often have social problems and develop depression that may lead to suicide. In Thailand, patients and their family members often believe that the symptoms are superstitious or they are “possessed”. Therefore, patients will seek help from a priest or “healer” for spiritual healing. Moreover, the condition may be episodic or fluctuating with intermittent remission. Some physicians may consider these patients as having convulsive disorders, hypochondriacs, factitious or conversion disorder. These patients may be accused of “faking” or “malingering” to gain attention from their family members or hospital personnel. Thus, they usually receive negative reaction from their relatives or attending physicians. The authors report herein a case of TP, 2 cases of TM and nine cases of TDt. The related literature is reviewed.

Cases Report

Case 1

A 66-year old man developed depressive episode for two years and was treated with mianserin 30 mg/d for depression along with quetiapine (QTP) 50 mg/d for his insomnia. When he was seen by one of the authors (DK), he was deeply depressed with masked face and hoarseness of voice. His movements were rigid with slow gait. However, his cognitive was normal and he was able to run his own business. A diagnosis of TP was made. QTP was immediately stopped and he recovered from depression in two weeks with tianeptine (SSRE-antidepressant) 37.5 mg/d, mianserin 30 mg/d, lorazepam (LZP) 2 mg/d. He also received trihexyphenidyl (THP) 4 mg/d for his TP symptoms, which disappeared six months later without having levodopa.

Case 2

A 28-year old man with mild anemia presented with symptoms of intermittent seizure-like (Fig. 2, 3), walking difficulty and repeated falls. At the age of 15 years, he was diagnosed as schizophrenia and was treated with haloperidol. He was hospitalized several times because of multiple suicidal attempts. Two years prior to the development of intermittent myoclonus (seizure-like), he allegedly had ingested more than 150 mg of haloperidol. He was thought to have “conversion disorder” by several physicians due to the fluctuation of his abnormal movement. Laboratory data were normal except low MCV 78 fl (normal range 80-100) and MCH 26 pg (normal range 27-34). A diagnosis of TM was made by one of the authors (DK). His movement disorders responded well to diazepam (DZP) 30 mg/d, THP 8 mg/d, CaCO3 3 gm/d and his psychiatric symptoms also improved with lithium (Li) 900 mg/d and clozapine (CZP) 12.5 mg/d. He was able to drive his car, play football, and help with housework. His TM symptoms returned two years later when either calcium or lithium was stopped but responded within two days after these drugs were resumed. He was finally stabilized on these medications during a 5-year follow-up.

Case 3

A 58-year old thin woman had a 30-year history of bipolar disorder with psychosis and she was treated with various AP drugs. She suffered from body twist, sustained seizure-like attacks when she was about to sleep and jerking of both arms and legs, which caused frequent falling for 2 years. She believed that these were “made action” or she was possessed. She presented with deep depression. She was mildly anemic and her blood test revealed hematocrit (Hct) of 36% (normal range 37-47), MCV 65 fl, MCH 21.5 pg, and MCHC 31.7 g/dl. A diagnosis of TM was made and she was treated with Li 600 mg/d, fluoxetine 20 mg/d, venlafaxineXR 75 mg/d, DZP 10 mg/d, THP 2 mg/d.
CaCO₃ 2 gm/d and iron supplementation while AP drugs were discontinued. Her mental symptoms and movement disorder responded well with this regimen when seen 10 months later.

**Case 4**

A 13-year old boy was a known case of Asperger syndrome and had received several atypical AP drugs (i.e., risperidone 4 mg/d, olanzapine 5mg/d), valproate 1000 mg/d and THP 2 mg/d for several years after becoming violent (both verbal and physical aggression). However, he complained of body stiffness and difficulty in swallowing due to laryngeal spasm and was unable to attend school after taking zisprazidone 80 mg/d for seven months. His laryngeal spasm responded well to LZP 4mg, CaCO₃ 3 gm/d, and THP 12 mg/d. He underwent electroconvulsive therapy (ECT) for his violent behavior. His mother reported that CaCO₃ was able to reduce muscle rigidity and laryngeal spasm. No symptoms recurred during a 9-month follow-up.

**Case 5**

A 19-year old woman was hospitalized because of aggression towards her mother with a knife and a suicidal attempt. Her past diagnosis was schizophrenia with conversion disorder and she was on typical and atypical AP drugs for two years. She was very thin with mild anemia. Her blood test revealed Hb 10.9 g/dl, Hct 35%, MCV 77 fl, MCH 26 pg. She also suffered from scoliosis and back spasm for one year. Her back pain, which occurred after taking AP drugs, was attributed to attention-seeking because she constantly demanded assistance from her family members. Such back pain and the fluctuation in severity of her symptoms led to the suspect suspicion of tardive dystonia. AP drugs were discontinued and she was given DZP 30 mg/d, CaCO₃ 3 gm/d, gabapentin 200 mg/d, and tianeptine 25 mg/d. Her condition improved within a few days and she no longer needed any assistance. She was discharged and was able to work. Her symptoms, however, recurred one month later because she stopped taking the medications. She responded well when these drugs were resumed and she was doing fine when she was seen at three months after discharge.

**Case 6**

A 19-year old male student developed severe shoulder and body pain after playing drum for hours. He was hospitalized and was diagnosed as having psychotic hypochondriasis. He received several antidepressants and antipsychotics, mainly olanzapine 10 mg/d for 2 years. His symptoms persisted with muscle rigidity. He was bedridden at home for 8 months and required physiotherapy. When he was seen by one of the authors (DK), he suffered from intolerable body pain that he wrote a suicidal note. He recovered from the pain when his previous antipsychotic medications were discontinued. Amitriptyline 10 mg/d and calcium supplement were given. He was doing well during the 5-year follow-up.

**Case 7**

A 40-year old thin woman presented with
emotional outbursts and violence. She had a 23-year history of “epilepsy and psychosis” and she was treated with AP drugs. She developed blephaloclonus, teeth grinding (bruxism) and jaw clenching 2 years before the current outpatient visit. A diagnosis of tardive dystonia was made and she was given carbamazepine (CBZ) 600 mg/d, CNP 4 mg/d, and fluoxetine 20 mg/d while AP drugs were stopped. Her movement disorder and mental symptoms improved and she had made a good recovery when seen 8 months later.

**Case 8**
A 42-year old female school teacher complained of talking difficulty from jaw spasm, pill-rolling tremors, and depression of 1 year duration. She had a 10-year history of bipolar with psychosis and was on various AP drugs. She was thin and anemic (Hb 10 g/dl, MCV 75 fl, MCH 21.6 pg, MCHC 28 g/dl). Her symptoms responded well to Li 600 mg/d, LZP 4 mg/d, tianeptine 37.5 mg/d, and THP 8 mg/d. Her condition was stabilized on these medications. She decided to return to her provincial hospital for further follow-up.

**Case 9**
A 25-year old man was admitted after becoming suddenly violent towards his mother. The patient had been diagnosed as schizophrenia with depression for 4 years. One year later after having various AP drugs, he developed neck dystonia, horizontal facial turning, and involuntarily walking backward occasionally. He also developed Tourette symptoms (he often shouted strange words repeatedly as reported by his mother). The patient was thin with mild anemia. He was very depressed and refused to leave his room. His mental symptoms responded to bupropionXR 150 mg/d, anafranil 50 mg/d, Li 900 mg/d, DZP 10 mg/d, valproate 500 mg/d, and CaCO₃ 3 gm/d, although some neck dystonia remained. He was able to leave home and meet friends. He was doing well when he was seen at 5 months after discharge.

**Case 10**
A 64-year old thin man presented with suicidal attempt and aggression. Two years ago, he was depressed and was treated with sertraline 50 mg/d, and quetiapine 25 mg/d was added when he showed signs of mania. He had also an 8-year history of Parkinson disease (PD) and was on levodopa/carbidopa. Two months before hospitalization, he developed aphasis due to laryngeal spasm. He was accused of making sexual advances towards the nurses when he tried to talk closer. His blood test revealed Hb 16.7 g/dl, Hct 49%, MCV 101 fl, MCH 34 pg. All symptoms improved and his voice returned when quetiapine was stopped and tianeptine 25 mg/d, CBZ 400 mg/d, LZP 1 mg/d were added. He was alert and active when seen 6 months later.

**Case 11**
A 64-year old man was a known case of bipolar disorder and he had been taking several typical and atypical AP drugs for 15 years. Five years before this current visit with one of the authors, he complained of unsteady gait with frequent falls. He also suffered from truncal muscle rigidity with severe shoulder and body pain. A neurosurgeon recommended an operation for “cervical spondylisis” but he refused the surgical treatment. All antipsychotic drugs were discontinued and he received gabapentine 400 mg/d, Li 600 mg/d, CNP 4 mg/d, LZP 4 mg/d, THP 8 mg/d, calcium, and vitamin supplement. His mental and physical conditions improved as well as his social life. He was in good health when seen 6 months later.

**Case 12**
A 72-year old man with a 20-year history of diabetes mellitus and hypertension was diagnosed as having mania for 4 years and was treated with fluoxetine 40 mg/d, valproate 1000 mg/d, CNP 2 mg/d, and quetiapine 25 mg/d. Two years later, he stopped taking these drugs because his condition was in remission. Six months before the outpatient visit, he suffered from body stiffness with shuffle gait. The brain MRI revealed mild cerebral atrophy. He was diagnosed with Parkinsonism and was on levodopa/carbidopa. However, his symptoms became worse and he could not walk because of leg weakness. He also complained of body pain, and leg jerking while sleeping. He was seen as “a complainer” by his family members. He was brought to the outpatient unit in a wheelchair because of ataxia and suicidal thoughts. The patient was thin with mild anemia. He responded well to tianeptine 37.5 mg/d, gabapentin 200 mg/d, CNP 2 mg/d, LZP 3 mg/d, THP 2 mg/d, and CaCO₃ 2 gm/d while levodopa/carbidopa was discontinued. He was doing well when seen 5 months later.

**Discussion**
The signs and symptoms of the presented patients fulfill the criteria for medication-induced movement disorders. In the present series, there were four women and eight men with age ranging from
13 to 72. Only three cases were under the age of 20 years (case 4, 5, 6). The youngest one was 13 years old and the oldest one was 72 years. Stiff body gait and hypokinesia in case 1 were symptoms of TP while brief and sudden repetitive movements observed in case 2 and 3 were characteristic of TM. Sustained involuntary movement disorders such as laryngeal spasm (case 4), back and body pain (cases 5, 6, 11, 12), bruxism and jaw spasm (cases 7, 8), torticollis (case 9), and aphonia (case 10) were symptoms attributable to TDt. It should be noted that TDt associated with Tourette syndrome as described in case 9 is unusual.

Several medications such as DA receptor blockers, antiemetic drugs, calcium channel blocker, tricyclic antidepressants (TCAs), serotonin-selective reuptake inhibitors (SSRIs), and various psychotropic drugs may result in a variety of tardive movement disorders(5,18,19). Symptoms are sometimes so peculiar (i.e., walking involuntarily backward as seen in case 7) that the patients may be mistaken as malingerers, psychogenic movement disorder (conversion disorder), or hypochondriacs. These symptoms usually disappear during sleep or at rest but emerge only when patients are in action or “action dystonia” or increase when patients feel nervous. Such wax and wane or periodic features often give the impression that the movement is faked or under the patient’s voluntary control.

Tardive dystonia (TDt) differs from tardive dyskinesia (TD) in that most cases of TDt have been reported in young male patients and it usually causes more distress, body pain and aching discomfort and disability(18,19). Moreover, TDt often develops rapidly after AP treatment. The focal symptoms of TDt may progress to more body areas and can persist for years after AP withdrawal. Although TDt symptoms often respond to anticholinergic drugs, TDt has little tendency to resolve and about half of the patients improve to some degree. On the other hand, the incidence and prevalence of TD are greater in older patients and appear to increase linearly with increasing dosage and duration of neuroleptic treatment. Increasing AP dosage may suppress TDt but will cause muscle rigidity or Parkinsonism. Anticholinergic medication may exaggerate TD symptoms. It should be noted that most TM cases have their symptoms occur at least 3 month after receiving AP drugs(5). Its prevalence is as high as 38% and most victims are male who receive a high dose of AP drugs as seen in case 1(5,20).

Janno et al reported nearly two-thirds of chronic schizophrenic patients suffered from AP drug-induced movement disorders(21). According to Ross et al, TD was found in about 40% of patients taking only typical AP drugs compared to 39% and 47% of those taking only atypical AP agents or both typical and atypical AP drugs, respectively(21). Gharabawi et al, in a recent study of 458 first-episode psychiatric patients, reported the lower annual rate of tardive dyskinesia with risperidone versus haloperidol(1). Annualizes rates were 0.72% with risperidone (mean dose 3.4 mg/d SD 1.80) compared to 1.87% with haloperidol (mean dose 3.2 mg/d SD 1.7). In the present series, the authors found three patients in whom abnormal movements occurred after chronic treatment with typical AP drugs (cases 1, 2, 7), five patients after receiving atypical AP agents (cases 3, 4, 6, 10, 11) and four instances (case 5, 8, 9, 12) taking both typical and atypical AP drugs. The present results confirmed that atypical AP drugs such as quetiapine at low dosage can induce TDt as noted in case 8 and 9. Additionally, in case 9, levodopa/carbidopa was found to exacerbate movement disorder as well as progressive weakness of legs. Most cases in the present series either required only low dosage of AP drugs or no longer need AP medications. The presented patients reported that anticholinergic drugs (such as THP) and CaCO3 high doses were able to reduce muscle rigidity and body ache. According to Schexnayder et al, 10 of 66 patients with non-affective psychoses responded to lithium alone while LZP was used to treat acute behavioral problems(23). In the presented patients, switching to benzodiazepine, mood stabilizer such as lithium, or using dopamine depleting drugs, anticholinergic agents, and antidepressants were helpful because most patients made a good recovery(24). Some authors suggested botulinum toxin for those with a local form of TD(6,25). Deep brain stimulation appears to be the most recent surgical therapy(29). It should be noted that calcium and iron supplement could improve symptoms of both TM and TDt as seen in the presented patients. Calcium salt may relieve muscle rigidity while anemia may aggravate movement disorders(12). Further studies regarding the role of calcium and iron supplement are recommended. Some authors suggested that tardive syndromes especially mild TDt might be more common than earlier thought as they can manifest in a variety of forms and in such peculiar features that clinicians may not be aware of these drug-induced extra pyramidal side effects(5,8). Hence, the vulnerability to developing tardive syndrome among patients who received AP drugs especially in the elderly must be emphasized. Although mild cases of TM or TDt may improve with time after AP discontinuation, the symp-
toms are often permanent and spread beyond the initial site of involvement. Therefore, most patients with severe dystonia have social difficulties and they often become despondent or suicidal as seen in the presented patients. It is important that clinicians should become familiar with these abnormal movements in order to detect early and provide prompt management. Using lower doses of AP drugs or alternative treatment is recommended for high-risk groups (i.e. children, elderly, patients with underlying brain trauma, PD, and those who are thin, anemia). The offending drugs known to cause such movement disorders should be used cautiously. All risks and benefits must be evaluated before initiating therapy. Monitoring for early signs of extra pyramidal syndromes will certainly prevent this iatrogenic effect.

Conclusion
A report is made on twelve cases of antipsychotic drug-induced tardive movement disorders that included a case of tardive Parkinsonism, two instances of tardive myoclonus, and nine examples of tardive dystonia. There were four women and eight men. The youngest patient was 13 years and the oldest one was 72 years. Most patients were thin and anemic. They were incorrectly diagnosed as hypochondriac or conversion disorder. All patients had social difficulties due to severe and abnormal movements and five of them had either suicidal thoughts or attempts. Antipsychotic drug was discontinued in most cases or switching to low doses of atypical neuroleptics. Benzodiazepine, lithium, anticholinergic agents, and antidepressants were effective in the treatment of tardive movement disorders while calcium salt and iron supplement appeared to be useful. The vulnerability to developing tardive syndromes among patients who received either typical or atypical antipsychotic drugs is emphasized and monitoring for early detection of this undesirable adverse effect is important for prompt and proper therapy.

References
19. Vandel P, Bonin B, Leveque E, Sechter D, Bizouard P. Tricyclic antidepressant-induced extrapyra-
กลุ่มอาการเคลื่อนไหวผิดปกติจากผลข้างเคียงของยาต้านโรคจิต รายงานผู้ป่วย 12 ราย

ดวงใจ กาชาดิถุ, บุรณี กาญจนถวัลย์

ภูมิหลัง: กลุ่มอาการเคลื่อนไหวผิดปกติจากยาต้านโรคจิตที่รับประทานมานหรือหยุดยาทันทีหลังจากใช้ยาติดต่อกันเป็นเวลาหนึ่ง หรือรับประทานยาบางสูง นานกว่า 3 เดือนขึ้นไป อาการมีหลายรูปแบบ เช่น classical tardive dyskinesia (TD) มีอาการกระตุกไม่หยุด ปลายนิ้วมือ หรือ tardive myoclonus (TM) มีอาการกระตุกไม่หยุด กระตุกอยู่ตลอดเวลา คอเอียง หลังโกง และอาการที่พบออกต่อกันมากน้อย มีการหลากหลาย ๆ ทำให้เสียหายหรือพูดลำบาก พูดไม่ได้ อาจเป็นที่ตั้งใจจะทำให้เกิดขึ้นได้ (Pisa syndrome) หรือ มีอาการหลอกหรือกระตุกหรืออาจมีอาการปวดที่แขน ขา หรือที่อื่น ๆ ที่อาจเกิดขึ้นได้ อาการดังกล่าวเกิดขึ้นเนื่องจากผู้ป่วยมีติดต่อกันดี ทำให้เข้าใจผิดว่าเป็นโรคหรือโรคภัยที่อื่น ๆ ทำให้เกิดอาการต้านทานใหญ่ขึ้น รู้สึกไม่สบาย หรือ ปวดมาก หรือ มีเจ็บ

วัตถุประสงค์: เพื่อรายงานผู้ป่วย 12 ราย ที่มีอาการกลุ่มอาการเคลื่อนไหวผิดปกติจากผลข้างเคียงของยาต้านโรคจิต TDI, TM และ tardive parkinsonism (TP) ซึ่งอาจทำให้ไม่เข้าใจว่าเป็น epilepsy, conversion หรือ hypochondriasis ผลกระทบศึกษา: ผู้ป่วย 12 ราย เป็นชาย 8 ราย หญิง 4 ราย อายุระหว่าง 13-17 ปี ทุกกรณีมีประวัติรับประทานยาต้านโรคจิตที่ช่วงนั้นเกิดขึ้น และรู้สึกไม่สบาย นานกว่า 1 ปี ผู้ป่วยมีอาการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขาอย่างต่ำกว่า หรือ อากาศ คอเอียง หลังโกง ปวดหลัง กินอาหารไม่ได้ ไม่ได้กิน หรือไม่ได้รับการกระตุกไม่หยุดของแขนขา

สรุป: เพื่อศึกษาความผิดปกติจากยาต้านโรคจิตที่เกิดจากผลข้างเคียงของยาต้านโรคจิต เพื่อให้การรักษาได้ที่เหมาะสม ยาต้านโรคจิตจึงจำเป็นต้องต้องใช้อย่างระมัดระวัง เนื่องจากมีกลุ่มอาการเคลื่อนไหวที่เกิดขึ้นได้ ตามข้อมูลที่ได้รับ