

Tardive Dyskinesia Revisited: A Clinical Priority Perspective-Diagnosis and Assessment (Part A)

Abstract

In this series of papers under the umbrella of tardive dyskinesia (TD), five major related issues are discussed pertaining to TD. These are integrated together. In Part A we evaluate how to diagnose, screen for physical signs and scales for tardive dyskinesia, and in Part B, we focus on the management. Tardive dyskinesia (TD) is a relatively new condition associated with abnormal involuntary movements caused by or aggravated by so-called “neuroleptic” drugs. Neuroleptics are used to manage psychotic conditions, as well as nausea and acid reflux, and latterly are prescribed as adjunct medications to depression and anxiety. Tardive dyskinesia (TD) has also become a major problem forensically, because of the challenge of management, the lack of patient’s being appropriately warned, and insufficient monitoring of patients at risk.

In this Part A series of articles we examine several special important priorities in TD.

- First, what is tardive dyskinesia and how does one make the diagnosis?
- The second issue is the need to regularly evaluate patients on neuroleptics because they are at risk for tardive dyskinesia. Measuring and monitoring for symptoms of tardive dyskinesia allows ensuring early detection. The author’s clinical STRAW test has thus far been seldom used, but it may be the best way to monitor TD over time. It appears an improvement over the standard test, the AIMS, as it is broader in ranking (0-10) and is the only scale that measures both frequency and severity, so that monitoring of change is more sensitive. In the series that follows, Part B, we emphasize management and theory, particularly high dose buspirone management, justify the dopamine super sensitivity hypothesis, and re-evaluate the neuroleptics in that context.^d

Keywords: AIMS; Atypical neuroleptics; Buspirone; Neuroleptics; SCT-Hans; Serotonin; Simpson-Angus; STRAW; Symptoms; Tardive dyskinesia; Tardive dystonia

^d DSM-4 R criteria allowed one month in geriatric populations but this is likely too little). Package inserts of drugs like metoclopramide stipulate 12 weeks.

Introduction

Tardive dyskinesia (TD) is a serious iatrogenic prescription induced condition, associated with abnormal involuntary movements. We know today that it is caused by or aggravated by so-called “neuroleptic” drugs. These are usually used to manage psychotic conditions, as well as nausea and acid reflux, and latterly are prescribed as adjunct medications to depression. The term “tardive” refers to the delay in the condition after receiving neuroleptics. “Tardive” dyskinesia often takes years to manifest fully, but might show itself initially at minimum after taking neuroleptics for three to four months. A very early use of the term Tardive dyskinesia was by Crane in 1968 [1] and warnings about TD, appeared already in USA pharmaceutical package inserts in 1971 [2].

Indeed, tardive dyskinesia (TD) has also become a major problem forensically, for three reasons:

- It is sometimes an insuperable challenge in management and misinterpreted as being “incurable” because, at times, it is irreversible and without consistent responsiveness to medications.
- Patients are of often not warned, and the condition is missed till late or not diagnosed.
- Clinicians do not monitor patients on neuroleptics, and do not recognize the need to refer their clients to experts at the first signs of difficulty: Early diagnosis and interventions are important.

TD manifests differently and tardive syndromes may persist for months or years after drug withdrawal and in some patients, the TD is irreversible [3,4]. An increased incidence of undiagnosed involuntary movements began in the 1950s after the development of antipsychotic medication. Many more involuntary movements began to be reported but they were

Review Article

Volume 6 Issue 2 - 2016

Vernon M Neppe MD, PhD, FRSSAF, DFAPA, DPsM, MMed, Seattle, WA*

¹Director, Pacific Neuropsychiatric Institute and Exceptional Creative Achievement Organization, USA

²Executive Director and Distinguished Professor, Exceptional Creative Achievement Organization, USA

³Adj. Professor, Department of Neurology and Psychiatry, St. Louis University, USA

***Corresponding author:** Vernon M Neppe, Director, Pacific Neuropsychiatric Institute and Exceptional Creative Achievement Organization, Seattle, Washington, USA, Tel: 206 527 6289; Email: psyche@pni.org; www.pni.org^{abc}

Received: June 16, 2016 | **Published:** June 29, 2016

^a © Exceptional Creative Achievement Organization.

^b Declaration: I lectured for many years on buspirone for Bristol-Myers during which I tried to provide balanced, useful information. In this instance, I studied the neuropharmacology of buspirone in enormous detail and this allowed me, inter alia, to make this tardive dyskinesia discovery. The tardive dyskinesia research was initially funded through a small independent research grant from Bristol-Myers during the late 1980s / early 1990s.

^c My grateful acknowledgements to the readers, editorial assistants, and referees, namely Dr Michael Norden, Dr Jean Adcock, Dr Stanley Schiff, Suzan Wilson, Jacqueline Slade, Lis Neppe who were involved in at least components of these articles or in all of them.

not initially diagnosed as due to any drug because there always had been prior reports of a much less common condition called “spontaneous” dyskinesia (SD). SD when just based on symptoms might, at times, be indistinguishable from TD. SD may manifest differently and has often been regarded as “idiopathic” which means the cause is unknown. So when more movements began to arise, they were apparently regarded initially possibly as one of those spontaneous” dyskinesia [5]. Ironically, in 1955 [6], chlorpromazine was reported to improve these movements after an initial 1954 report [7]! This, in retrospect, was likely a temporary phenomenon sometimes seen with increases in doses, though the changes over long time periods would ultimately worsen the condition.

In February 1958, the very powerful neuroleptic Haloperidol [8,9], revolutionized the treatment of psychosis because it was very potent and was therefore became the most popular agent. It had profound clinical effects, [10,11] but, possibly remains possibly the greatest ever cause of TD.

What is Tardive Dyskinesia? Section 1 [5]^e

Abstract

We discuss what tardive dyskinesia is, and how one makes a diagnosis of tardive dyskinesia (TD). TD is a chronic, sometimes irreversible, condition, associated with the long-term use of neuroleptics. It is linked with abnormal involuntary movements of parts of the body. Tardive dyskinesia (TD) is a condition linked with abnormal involuntary movements of parts of the body. It is a chronic disorder associated with the long-term use of neuroleptics. TD often takes years to manifest but might manifest within months of initiating the neuroleptic. The movements manifest most commonly in the mouth, cheeks, lips, tongue and jaw with grimaces (“orobuccolinguomasticatory” movements) but might show themselves anywhere in the body, most commonly in the upper and lower limbs and in the trunks and usually in several parts of the body to varying degrees.

^e Vernon M Neppe MD, PhD, Pacific Neuropsychiatric Institute, Seattle, WA.

Table 1A: Tardive dyskinesia Orobuccolinguomasticatory movements.

- a. The most common movements
- b. Involved the mouth, cheeks, lips, tongue and jaw
- c. Can be grimaces e.g. puckering, pouting, smacking, even “rabbit” movements (?) variant

Movements are characteristically writhing and may appear jerky and more rapid at the distal arms and less smooth than the proximal choreiform or athetoid movements of other conditions. They can be asymmetric. They often manifest distally (e.g., in the hands) as opposed to proximally (e.g., in the shoulders) where the movements are faster and less choreic. The movements can, however, manifest in many different ways, but they are always involuntary to a degree (some patients suppress them, for example, by holding their hands tightly, or camouflage them e.g., by using a yo-yo in their arms or claiming to be chewing gum).

Movements can vary: Puckering, pouting, smacking, blinking, persistence of various neck muscles movements, biting, clenching, mouth opening and lateral movement jaw movements are all variants, as are choreiform, athetoid or rhythmic (sometimes stereotypical) abnormal involuntary movements. The frequency and amplitude of movements in TD are therefore dissimilar in each patient, and fluctuate widely in the same patient at different times. This is why we need to assess severity of the movements and measure frequency of the movements over time (Table 1B).

Table 1B: Tardive dyskinesia basics.

- a. Chronic disorder associated with the long-term use of neuroleptics.
- b. Abnormal involuntary movements can occur in any part of the body
- c. Most commonly movements are in the face, upper and lower limbs and to a lesser degree in the trunks (e.g. tardive breathing)
- d. Individual muscle movements vary in severity in the same patient
- e. Variable impairments, but consistent within the patient.
- f. Severity range varies
- g. Movements do not occur during sleep.
- h. Patient is always fully conscious

TD usually has a delayed onset and the intensity of the syndrome may fluctuate over time. The most serious aspect of TD is that it may persist for months or years after drug withdrawal and in some patients, the TD is irreversible [12]. The movements vary in severity: Most times they are usually mild and not distressing. Sometimes patients are unaware of the movements.

But the more severe patients certainly are, even if family members have drawn attention to them. This therefore may lead to secondary psychopathology: The patients are embarrassed, ashamed of their movements, try to camouflage them and become socially withdrawn. Interactions cause anxiety and may aggravate movements (Table 1C).

Table 1C: Tardive dyskinesia movement variations.

- a. characteristically writhing
- b. may be jerky and more rapid
- c. often distally in limbs
- d. asymmetric
- e. less choreic and smooth than proximal choreiform or athetoid movements manifest in many different ways.
- f. always involuntary
- g. some patients suppress them, e.g., by holding their hands tightly, or camouflage them e.g., chewing gum
- h. Movements variants: blinking, persistence of various neck muscles movements, biting, clenching, mouth opening and lateral movement jaw movements
- i. The frequency and amplitude are dissimilar in each patient, and fluctuate widely in the same patient at different times.
- j. Tardive akathisia is a relatively rare but uncomfortable variant.

TD develops in association with neuroleptic use usually over years, but at minimum over three to four months. (DSM-4 R allowed one month in geriatric populations but this is likely too little). Even package inserts of drugs like metoclopramide stipulate 12 weeks [13]. The onset of TD can be during exposure or within a month of withdrawal (or two months if it was a depot neuroleptic) [14]. Because this is a potentially incurable condition, practitioners should advise the patient about the possibility of the condition manifesting, even at the start of neuroleptic prescriptions and regularly thereafter. They should ensure they are monitored for TD by an active TD examination such as the STRAW [15]. I originally developed the STRAW specifically in 1989 in a severe TD patient because there was no adequate scale to monitor movements in both severity (from 0 to 10!) and frequency during set time periods [16]. Severity varies greatly: Usually the manifestations are mild but sometimes the condition is profound. The movements do not occur during sleep, and the patient is always fully conscious.

Diagnosis of tardive dyskinesia is longitudinal (over time) because acute or short-lived (e.g., over less than a month) movements of these kinds can be due to withdrawal of neuroleptic: That is sometimes called Neuroleptic Withdrawal-Emergent Dyskinesia (NWED) and this NWED has nothing to do with TD and is time limited lasting up to 4-8 weeks. Beyond that time period, a diagnosis to TD should be considered. Other movements of the mouth can also have nothing to do with TD: the movement of chewing made by chewing-gum sometimes looks like TD. There is a spontaneous group of dyskinesias, and rare progressive conditions, such as Huntington's chorea (which

may sometimes have a family history, and might have no history of neuroleptic medications), Sydenham's chorea, Wilson's disease and chorea associated with antiphospholipid syndrome [17] must be considered. Diagnosis is facilitated by video recording, and this way examining movements several times per day as the severity will vary, but requires proper evaluations preferably at every appointment using appropriate standardized measures: The author has been using the STRAW scale.

Here is one videotape, not from a patient of mine for HIPAA reasons, but from the Internet in the public domain.

<https://www.youtube.com/watch?v=QYYx1mZDp-Pw#t=35.592188>

TD is a chronic disorder involving the brain's extrapyramidal motor system that is almost always due to neuroleptics. It therefore is involved with the broader group of "basal ganglia" disorders. Amongst these are Parkinson's disease, acute extrapyramidal disorders like rigidity due to neuroleptics, Huntington's chorea, and even subtle less usual conditions just mentioned here, like "rabbit movements of the mouth", oculogyric crises of the eye, and neuroleptic malignant syndrome. Parkinson's manifestations may occur far more commonly as part of neuroleptic drug-induced extrapyramidal manifestations and this may include possibly the most common side-effect of all namely akathisia the sensation of having to keep moving and not being able to keep still. Whereas these are entirely different conditions to TD, they should serve possibly as a warning that the patient may be at greater risk for TD because the "body", so to say, is telling us them "*I have reached close to my dopamine limits or even overreached them*".

Conversely, usage of “dopamine agonist” drugs such as Levodopa and its variants might aggravate the psychosis in psychiatry. In Parkinson’s disease, these dopamine agonist medications are a staple, but have their own side-effects. Like TD, treatment many involve stopping or lowering the medications, but “anticholinergic” medications such as benzhexol helps relieve the movements in these drug-induced parkinson’s conditions^f, yet may long-term aggravate TD.

Important points

Diagnoses at greater risk for TD

But most importantly, in my opinion, those patients who are not biologically psychotic are at great risk: Patients with mental retardation, brain damage, seizures, paroxysmal brain conditions and narcolepsy can all easily be misdiagnosed at times as having psychotic conditions like schizophrenia. But they do not tolerate antipsychotics and have side-effects like sedation or extrapyramidal features at much lower doses than in a schizophrenic patient. That should be a clue, something I have emphasized for decades [18-23]. I speculate that we also might

see TD more commonly in patient’s labeled “bipolar disorder”: This might be because some of these patients are prescribed high doses of neuroleptic during an acute phase of mania, for example. The patient might then be inappropriately maintained on much higher doses of neuroleptic than they need: they might not need any longer because they are no longer floridly psychotic. The same non-toleration principle might apply for hallucinogen-induced psychoses. I regard these biologically as different from chronic psychoses, which, I argue, is why some of these patient respond to anticonvulsants [18-22,24]. In both these diagnostic examples, the biological non-toleration of neuroleptic doses produces potential side-effects [18,22,23]. Possibly the most dramatic and serious side-effect is TD.

The predisposing factors we should avoid in TD

We must recognize that smoking and diabetes correlate with TD. We also know that older age may predispose though this may be because of other confounding factors. And anticholinergic drugs may aggravate the TD condition: This is a problem because we commonly see that recommended, even on this list (“my neurologist colleague suggested ...”).

^fSome conventions use the capital P for the idiopathic Parkinson’s disease, and small-case p for drug-induced parkinson’s conditions. This is similar to the convention of using upper-case letters for branded drugs; and small-case for generic compounds as that is the chemical name.

Table 1D: Predisposing factors to tardive dyskinesia:

Usually quoted are:

- i. Dose times duration equation [25-29] (see the modified algorithm below)
- ii. Female (5.8% vs 10.6%; overall 8.2% [30] (relating to numbers presenting or diagnosis?)
- iii. Incidence varies widely depending on drug [31-37] (? D2 /3 selectivity may predispose)
- iv. Ethnic differences (higher incidence in black and Asian population) [38-41]
- v. Family history (likely ? because of misdiagnoses across families)
- vi. Smoking [42-44] (some dispute)
- vii. Diabetes [45,46]
- viii. Elderly [47-55] (need lower prescriptions usually)
- ix. Organic / Mental retardation [56,57] (need lower prescriptions usually) Acute neurological illness [34,38] (need lower prescriptions usually)
- x. Genetic polymorphisms D2/3; S2A [59] (e.g. particularly 2D6 poor metabolizes may require lower prescriptions usually)

I regard far the most important factors predisposing to tardive dyskinesia as:

- I. Dose times duration equation: The higher the dose and the longer the duration, the more the risk.
- II. Too high a dose: Doses vary depending on the condition e.g. If a patient has a functional psychosis like schizophrenia, they tolerate the drugs more easily.
- III. But adjustments must be made, at times because of variations: Acute mania involves greater toleration; patients with organic disease receive less.

IV. I suggest the following modified algorithm: (Dose *a) * (Duration of treatment •b) * (Diagnostic scaling * c) * (Severity * d). The variables are a, b, c and d as there may not be an easy consistent relationship.

Speculations

I mention here two speculative aside statements, based on my empirical clinical experience of TD, and also on forensic cases I’ve encountered

Greater risks of neurological conditions

I postulate that those *at greater risk for TD are not biologically typically chronically psychotic*: in other words, they've received too high a dose of neuroleptic for their specific condition. What is known is we can likely guesstimate risk recognizing that the greater the size of the dose and the longer the duration in months and years of taking the medication are multiplicative risk factors. However, I propose that biochemical-electrical factors reflecting lowered toleration of neuroleptics make some patients even far more at risk [18-21,60]. Effectively, when the dose for that patient is relatively too high the risk increases and often the choice of neuroleptic may be wrong.

Patients with TD on SSRIs

And here is something even more controversial: Repeatedly, I find that much TD has been triggered by the group of antidepressants called "Selective Serotonin Reuptake Inhibitors", better known simply as "SSRIs". Now you would think "maybe sertraline being more dopaminergic would be different", but I regard this as a class phenomenon in SSRIs and far more so than any other antidepressant group possibly because SSRIs characteristically produce relatively very high pharmacological serotonin levels and the body requires appropriate adaptation more than with any other antidepressant [24]. In my opinion, I don't think it is a product of SSRIs just being more commonly

used: I postulate it is a mobilizing effect of SSRIs on TD. I am only now reporting this neglected area, but at this point have probably encountered tens of cases though they are clinical and uncontrolled. I strongly speculate that we should avoid SSRIs in patients on antipsychotics.

Ultimately, tapering of the SSRI (and if needed replacing with an SNRI) may be required to maximize results (you should still see improvements even on the SSRI but not as completely, in my opinion) and such tapering requires many, many months usually and is very slow and carefully monitored. The possible aggravation by SSRIs implies caution. In my experience, this SSRI aggravation by at least some of the SSRIs might occur predictably and always once the TD has developed. And it's not only drugs like sertraline, well documented for dopaminergic activity. It seems to be every SSRI. I have not seen this affect with any other antidepressant, but then SSRIs appear far the most prescribed of the antidepressants that I've been exposed to.

Difficult diagnoses

Every so often, I am referred cases labeled tardive dyskinesia who do not have tardive dyskinesia. The diagnoses vary and include patients with dystonias, and those who have had cerebrovascular events. They will not respond to buspirone, of course, and so proper diagnosis is important (Table 1E).

Table 1E: Differential diagnosis of TD

- a. Dyskinetic or choreiform movements
- b. Withdrawal dyskinesias (can last up to 4-8 weeks)
- c. Spontaneous dyskinesias (rare: some say as many as 5% but in TD if that figure were correct and this too is high but based on equivalents, it is 20%)
- d. Other dyskinesias e.g. Huntington's chorea, Sydenham's chorea
- e. Psychogenic movements (these are rare; they may be more common in forensic cases; they often have histories of other conversion or psychiatric features so the psychodynamics must be correct).
- f. Wilson's disease
- g. Chorea with antiphospholipid syndrome

Not dyskinetic, but can be mistaken occasionally for TD

- a. Seizures (usually are very different but not always e.g. myoclonic phenomena; seizures occur during sleep, with loss of consciousness at times, and often stereotypical))
- b. Tardive or other dystonia (sometime an endpoint of the TD; but biologically different based on responsiveness.)
- c. Narcolepsy with Cataplexy (rarely cataplectic events can look like movement disorder)
- d. Organic base (movements can be variable)
- e. Parkinson's (at times, misdiagnosed)
- f. Habits (sometimes minor movements or tics have been around for years)
- g. Combinations

Tardive dystonia is different from TD

Some chronic, long-standing patients with severe tardive dyskinesia also develop tardive dystonia —persistent muscular spasm reactions. Dystonia manifests as stiffness in the limbs and skeletal structure. In one variant, it might even involve leaning backwards and it can produce significant distortions of posture or deformity. The dystonias apparently only marginally respond to buspirone, I postulate, not because of the dystonias themselves, but some dystonic improvement may secondarily

slightly occur because the dyskinesia has so improved that the spasms may lessen. Tardive dystonia should be managed by a neurologist specializing in movement disorders. Management is individualized and complex. I've not seen tardive dystonia responding to buspirone. The mechanism is likely very different from TD. Dystonia does not involve a reversible process linked with dopamine super sensitivity. Buspirone is not therefore a treatment for tardive dystonia as it's not due to dopamine supersensitivity like TD is.

Evaluation by the STRAW in Tardive Dyskinesia: Section 2 §[6]

Abstract

The second issue is the need to regularly evaluate patients on neuroleptics because they are at risk for tardive dyskinesia. Measuring and monitoring for symptoms of tardive dyskinesia allows ensuring early detection. The clinical STRAW test has thus far been seldom used but it may be the best way to monitor TD over time, and appears better than the AIMS as it is boarder in ranking (0-10) and is the only scale that measures both frequency

and severity.

Monitoring for tardive dyskinesia

Because of the inherent and dangerous risk, we need to diagnose early. This means that every time I see an outpatient on neuroleptics I try do formal TD testing (e.g., the STRAW and several other tests) though if I see a patient more frequently than once in that week, I do not. Obviously, we must monitor progress over time of the TD as well. It's critical to monitor TD so as to observe changes early and ensure the condition does not progress (Table 2A).

§ Vernon M Neppe MD, PhD, Pacific Neuropsychiatric Institute, Seattle, WA

Table 2A: Tardive dyskinesia movement changes

- i. Stress exacerbates
- ii. Medical or psychiatric condition exacerbates
- iii. Medication relieves e.g. buspirone
- iv. Missing medication aggravates
- v. Rarely certain medications or supplements can exacerbate

Often video monitoring can benefit understanding the changes.

Table 2B: Tardive dyskinesia movement monitoring

- i. Video monitoring is useful in any extrapyramidal disorder
- ii. Monitoring should be properly done using STRAW and AIMS, at minimum.

The following should logically be looked for in a good scale:

Table 2C: Good Tardive Dyskinesia measurement scales should

- i. Measure severity and apply a large range of severity
- ii. Measure frequency of movements and apply a large range of measures
 - a. Occurrence over the day.
 - b. Rank changes with easy to perform monitoring
- iii. Should be specific for TD

What options are available: There are four that are logical (Table 2C). Three are discussed briefly. But the STRAW is so important that it is detailed.

Table 2D: Measurement options for TD

- a. AIMS scale
- b. Simpson Angus
- c. SCT Hans
- d. STRAW

I routinely perform all four measures, every time I see a patient with movement disorder or who is on neuroleptics. It is difficult to justify not doing so clinically and forensically. The extra data helps compare these tests, and provided a good evaluation is done, I find I rely by far, most on the STRAW. However, once one is evaluating

a patient the extra information does not take much longer. These four are summarized in Tables 2D through 2G.

The AIMS is the standard but limited in range and therefore sensitivity, non-specificity and not measuring frequency of movements (Table 2D).

Table 2E: TD measurement AIMS scale (Abnormal Involuntary Movement Scale)[61-63]

- i. Well-known, non-specific EPS
- ii. Commonly used
- iii. Golden 1987 ?
- iv. Measure Severity: +
- v. Large Range: No 0-4
- vi. Measure Frequency: No!
- vii. Measure over time? Yes
- viii. Rank targeting TD? No
- ix. Easy changes: No?
- x. TD adapted: No?

Seldom recommended unless for research is the Simpson Angus. It does include features not in The STRAW and targets more conditions like Parkinsonism and akathisia (Table 2E).

Table 2F: TD measurement Simpson Angus scale

- i. Most have heard of it
- ii. But not commonly used [15,26,64,65]
- iii. Measure Severity: +
- iv. Large Range: No 0-4
- v. Measure Frequency: No!
- vi. Measure over time? Yes
- vii. Rank targeting TD? No
- viii. Easy measuring changes: No?
- ix. TD adapted: No?

Likely never recommended unless for research is the SCT HANS. The STRAW was adapted from it.

Table 2G: TD measurement SCT HANS scale ? 1989

- i. Most have never heard of this Danish scale (difficult to even find citations now) [65]
- ii. Almost never used
- iii. Measure Severity: +
- iv. Large Range: Somewhat 0-6
- v. Measure Frequency: No!
- vi. Measure over time? Yes
- vii. Rank targeting TD? No
- viii. Easy measuring changes: No
- ix. TD adapted: Yes maybe

I use the STRAW all the time in patients to evaluated TD.

Table 2H: TD measurement STRAW scale of measurement

- i. Seldom heard of (Neppe, 1989) [16]
- ii. Routinely used at PNI for a quarter century with great success. [15,66]
- iii. Measure Severity: Yes!
- iv. Large Range: Excellent 0-10
- v. Measure Frequency: Yes! 0-10
- vi. Measure over time? Yes, easy
- vii. Rank targeting TD? Specific
- viii. Easy measuring changes: Yes
- ix. TD adapted: Yes, definitely

Consequently, Neppe places the STRAW for TD in perspective (Table 2H).

Table 2I: STRAW scale of measurement perspective

Advantages

- i. Sensitivity
- ii. Easy to use
- iii. Obtain single score: Severity * Frequency

Disadvantages

- i. Easy to train but must like all tests must train
- ii. Consequences
- iii. Useful sensitive monitoring clinically and in research.

Perspective

- i. More specific
- ii. Use: Neppe compares it each time with all other tests
- iii. Some items e.g. EPS, akathisia, and salivation better with others.

The STRAW as a major measure for tardive dyskinesia

Our cases have been carefully monitored using an objective scoring evaluation called the STRAW [67-69] that I developed specifically for tardive dyskinesia. The STRAW is the only rating scale that measures both Time and Severity of the dyskinesia, applying several techniques each on a 0 to 10 scale. Additionally, we also use several other tests for comparison that are less sensitive (e.g., AIMS, SCT-Hans, Simpson-Angus).

The STRAW description [15]

The STRAW is an objective clinical examination differentiating subtle differences in tardive dyskinesia because adequate reliable measures were unavailable. The STRAW was first used in the landmark Neppe case description of high-dose buspirone in Tardive Dyskinesia (TD) in 1989. The STRAW is a standardized administered movement disorder evaluation. Uniquely, it uses a 10-point scale multiplying *frequency* (proportionately timed component) and *severity* scores. The most severe of the movements in the head, axial skeleton, and limbs (0-10 severity) are closely followed for extraneous movements incorporating many features of the AIMS, SCT-Hans and Simpson-Angus. It's routinely used on patients receiving neuroleptics, or for those at risk for any movement disorders, obtaining baseline and follow-up measures of change with medications and other alleviating or accentuating phenomena. STRAW scores are compared with the also routinely performed AIMS, SCT-Hans and Simpson-Angus Examinations and appear the most applicable TD and superior to these in TD evaluations.

STRAW is an acronym: Five *activity* evaluations each out of 10 make up 50 (the TRAW) loaded equally with scores at *rest* (50) (the S of the STRAW) (total 100)

"S": sitting at rest (converted to 50)

Activity each 10: *"T": tapping; "R": reading; "A": arms outstretched; "W" is for writing; also "W" for walking (gait).*

Activating procedures also evaluate power, gait, tone, resistance, mouth opening and tongue protrusion. Usually all four of these tests are used. They're different but widely overlapping evaluations are routinely performed at the Pacific Neuropsychiatric Institute. We have accumulated an enormous amount of clinical data on a wide variety of patients.

We evaluate patients necessarily for movement disorders under the following circumstances:

- a. Any patients on neuroleptics or on whom these are being initiated (to obtain a baseline). These patients are then

monitored to ensure appropriate early treatment for drug induced extra-pyramidal conditions such as parkinsonoid features with rigidity, akinesia and tremor plus akathisia and tardive dyskinesia and dystonia.

- b. Patients requiring evaluation for movements given any of baseline phenomena on examination, previous high risk for tardive dyskinesia and extrapyramidal symptoms or muscle weakness such as in myasthenia and sometimes other pertinent neurological conditions.
- c. In addition, the historical information obtained during the clinical consultation may reflect discomfort the patient has had recently relating to movements of any kind.

The following techniques have been used to achieve appropriate movement evaluations objectively and rapidly, as much of it can be done during the routine interview and evaluation without the patient being aware of being evaluated specifically for movement disorders. Coincidentally, this has proven useful to compare three major tests for movement disorder. The criteria for all of these tests, where applicable, allow comparisons and data for standardization of tests. However, they are all used clinically, because commonly they do not require much additional work as they all assess similar movements, although there are specific differences which is why more than one has been used. The STRAW and AIMS procedures are performed as well as evaluations relating to the modified scoring of the SCT HANS. The AIMS evaluates blink rate, salivation and glabella tap which the STRAW does not.

Though all measure every kind of movement disorder, there are different emphases:

- i. The STRAW is more focused to tardive syndromes, the AIMS to acute extrapyramidal disease.
- ii. The Simpson-Angus test is also routinely performed in the event of pathology relating to other tests.
- iii. We perform all because each adds something to the assessment.

Standardization

- a. The measures at rest are at times of relaxation, before or after the active procedure.
- b. The observation is unobtrusive unless we want to evaluate specifically under special circumstances e.g., reading or writing or gait.

- c. The chair used is hard and firm and by standard, without arms.
 - d. The patient is evaluated using standard conditions in relation to rest movements, sitting in the chair, with legs slightly apart and feeling comfortable, with the feet on the floor.
 - e. Arms are at rest in a position of selected comfort for the patient, in at least two positions, most usually resting on the lap and lower limbs, or unsupported at the side.
 - f. The mouth and gums are evaluated to exclude confounding issues such as gum, candy and dentures as well as oro-bucco-linguo-masticatory movements.
 - g. Mouth opening is observed with the tongue at rest and protruded looking for abnormalities of tongue movement.
 - h. Tapping with the hand is rapid, reflecting both separate hands and togetherness.
 - i. Gait is evaluated in as natural a context as possible with the patient's entry and exit as well as postural elements pertaining to seating and standing. This also requires the patient to turn to negotiate the chairs.
- iv. "W" is for writing;
 - v. "W" for walking or gait is a second 10 second W measure.
 - vi. The activating procedures also include evaluate muscle power and gait, tone, and resistance, mouth opening and tongue protrusion though not specifically scored

Three body sections are measured for severity: *the head, the axial skeleton, and the limbs*. Each body section is rated between 0 and 10 in severity. *In practice, the most severe of these three rankings is the one that is most closely followed over a period of time for tardive dyskinesia.* The STRAW timing system is multiplied by the STRAW severity, giving a total score out of 1000. It is thereafter divided by 10 to score out of 100. This gives an index of both severity and duration of particular physical signs.

A similar ranking degree is allocated for the STRAW as for other scales measuring the same movements. The difference is that the STRAW recognizes that at the higher scale of measurements, the movements should be more differentiated and there are slightly more options at the lower scoring level. For example, in the AIMS: 0 = none, 1 = minimal, 2= mild, 3= moderate, 4 = severe. Similarly, the STRAW scoring: 0 = none, 1 = minimal, 2= mild, 3= moderate, 4 = severe. Therefore the standardizations for the same movement would be the same. But what happens to 5 to 10 scores? We need to differentiate higher levels of severity and the STRAW does this: 5= Very severe, 6= Extremely severe, 7= Profound, 8= Very profound, 9= Exceedingly profound and 10= Most profound ever seen or possible.

This ranking may seem like overkill and for most patients it is, but there are times when there is a degree of severity of the major movement being exhibited that is so strong that it needs to be differentiated otherwise one would have difficulty demonstrating improvement? This is what happened with the first reported case of tardive dyskinesia treated with high dose buspirone therapy. So most of the time even on the STRAW, the scores of 0 to 5 are quite sufficient. Similarly, we felt that scores up to (say) 6 were insufficient when very severe, and this is why we *adapted* the SCT Hans score to 0-10 range, noting that the STRAW spontaneously during "rest" evaluations (i.e. not specifically asking to elicit specific movements) uses the same bodily areas as the SCT Hans [70].

Thus the STRAW has several advantages over other tests.

- a. It takes no longer than other major tests, yet generates at times, unique information.
- b. It is especially useful in tardive dyskinesia assessments.
- c. It has a range of severity that is wider than other movement disorder evaluations (0-10).
- d. It also combines in duration of time that a physical sign of movement disorder is manifesting: In this instance, "all the time" a specific criterion is being evaluated is equivalent to 10, with the mathematical ratio of "time of any movement irrespective of severity"/ total time of movements being assessed under those circumstances being objectively calculated. This is usually a global (whole body) ratio score that can be exactly timed, and therefore can be very

The STRAW components

STRAW is an acronym for a new technique of evaluating involuntary movements, particularly tardive dyskinesia. Neppe developed the STRAW in the early 1990s because of the non-availability of adequate measures which would reliably differentiate subtle differences in severe tardive dyskinesia, and which could be easily scored within a 10% range by several different raters as well as to obviate the conundrum of Severity versus Duration of movements, and these have been found to very different. The STRAW therefore has two components, a timing component and a severity component. The STRAW timing system involves equal maximum scores of 50 for activation and 50 for rest. The key to the STRAW is the timed component. The timing component is scored out of 100 based on a time period using the criterion of all the time the patient was present.

Tremor and epileptic seizure are not included as involuntary movements, although like all movements and abnormalities they are noted. Half the time is at rest is the "S" for sitting at rest while relaxed, not under stress. and standing - the score is a *rest score*. Convert these rest time measures to proportion of time out of 50 (such as at rest). e. g. 40 seconds of movements in a selected 300 second interval = $60/300 \times 50 = 10$

Background to the STRAW

The five evaluations during activity are each out of 10 making up 50 for activity (the TRAW) loaded equally with the 50 for sitting at rest (the S of the STRAW).

Activity involves

- i. "T" for tapping for both the right and the left hand out of 10, separately and together;
- ii. "R" for reading something and the involuntary movements are watched;
- iii. "A" is for arms outstretched and the movements evaluated

- accurate in terms of inter-rater and intra-rater reliability.
- e. The Severity multiplied by the Timing is calculated producing a score out of 100 as the result has been divided by 10. Again, this introduces concepts of severity and duration.
 - f. STRAW evaluations take into account that anxiety may

exacerbate though this does not modify the score unless there are extraneous movements.

We now give an example of a score sheet for no involuntary movements. To assist the default score of 0 is on the electronic scoresheet already, and can be changed. This constitutes a normal examination for these four tests.

Straw Examination for Involuntary Movements

This is a timed and severity neurological evaluation for involuntary movements

At Rest

- a. S - SITTING AND STANDING - out of 50; SCORED 0 severity, and 0 timing.
- b. ACTIVATION PROCEDURES; SCORED
- c. T - TAPPING WITH RIGHT AND LEFT HAND - out of 10; SCORED 0 severity, and 0 timing.
- d. R - READING - out of 10; SCORED 0 severity, and 0 timing.
- e. A - ARMS OUTSTRETCHED - out of 10; SCORED 0 severity, and 0 timing.
- f. W - WRITING - out of 10; SCORED 0 severity, and 0 timing.
- g. W - WALKING - out of 10; SCORED 0 severity, and 0 timing.

Straw Timing Score Total IS 0. (0 is normal; maximum is 100)

SEVERITY score is 0 / 50 at rest and 0/50 with specific active tests (0 is normal; maximum is 10)

COMBINED SEVERITY TIMING STRAW SCORE = TIMING * SEVERITY / 10 = 0.

(0 is normal; maximum is 100).

The STRAW incorporates many of the features of the AIMS below and the SCT HANS below.

The ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS) is also used in this evaluation.

The AIMS uses a 0 to 4 scale based on symptom severity.

0 = none, 1 = minimal, 2= mild, 3= moderate, 4 = severe.

Unfortunately there is more than one AIMS examination available. This is what we use:

- i. Seating - hands supported. Score 0
- ii. Seating - arms unsupported. Score 0
- iii. Opening of mouth and observation of tongue at rest. Score 0.
- iv. Opening of mouth and observation of tongue during movements. Score 0.
- v. Tapping with the thumb and each finger using right, left (and both) hands. Score 0
- vi. Flexion and extension of each arm passively. Score 0
- vii. Standing up. Score 0
- viii. Active outstretching of both arms. Score 0
- ix. Gait evaluation including turning. Score 0

Maximum AIMS score 36. Perfect score 0. Patient's score 0.

Other features in other AIMS for acute EPS (noted and scored as 0).

Tremor, Rigidity (done), Blink rate, Salivation, Bradykinesia, Postural reflexes, Dystonia, Pain soreness complaints, Restlessness observed and subjective.

This scale uses present and absent only. The AIMS is not one consistent test and has e. g. this variation.

Sct Hans Evaluation Modified.

This test involves severity evaluation of hyperkinesias, Parkinsonism, Dystonia and Akathisia.

Range 0 to 6. Neppe modification through to 10.

0 Absent, 1 Dubious, 2 Mild, 3 Mildly Moderate, 4 Moderate, 5 Moderately severe, 6 Severe, 7 Very Severe, 8 Extremely Severe, 9 Profound, 10 Extremely profound.

All anatomical areas are evaluated (jaw, tongue, lips, face, head, trunk, upper extremities, lower extremities) using

- a. Passive Hyperkinesia Score 0
- b. Active Hyperkinesia Score 0
- c. Also evaluation for Parkinsonism.
- d. Global
- e. Facial Expression
- f. Bradykinesia
- g. Tremor
- h. Posture
- i. Arm Swing
- j. Gait
- k. Rigidity
- l. Salivation

Total Score 0, And Global Score 0.

D. Also evaluation for dystonia and akathisia

Acute, psychic, motor elements. Score 0

Finally evaluation for psychic symptoms

Sedation, Depression, Anxiety

These were performed within the mental status examination and were not incorporated into the SCT HANS score.

SCT Hans score MAXIMUM SCORE 40. 0 is normal.

Simpson-Angus Quantitative Assessment Of Motor Function.

Like the AIMS, this involves a 0 to 4 severity rating of the same degree but the criteria are better defined than the AIMS.

This test is not generally indicated unless there are clues as to abnormality.

- i. Gait with arm swinging. Normal. Score 0.
- ii. Arm Dropping. Raising hands to shoulder height, letting them fall: Free fall. Score 0.
- iii. Shoulder Shaking. Passive to and fro and external rotation of arm in held position. Ranking normal
- iv. Elbow rigidity. None. Score 0.
- v. Wrist rigidity. None. Score 0.
- vi. Head rotation. None. Score 0.
- vii. Glabellar tap. Normal blink response. Score 0.
- viii. Tremor. Normal. Score 0.
- ix. Salivation. Normal. Score 0.
- x. Akathisia, None. Score 0.
- xi. Maximum score is 20. Normal score is 0. Total score is 0.

Perspectives: Priorities for Evaluating Tardive Dyskinesia: Section 3

Far the most sensitive test for tardive dyskinesia is the STRAW for five reasons:

- a. It ranges in score from 0 to 10 allowing subtleties. Additionally what may be ranked severe will be scored the same as profound on the AIMS and Simpson-Angus scales.
- b. It measures not only duration (time) but also severity. This allows a composite score of how pertinent changes are. This is the only scale that does so.
- c. It incorporates all the overt, obvious features in movement disorders allowing for an easy and obvious way to rank severity and using a watch and dividing the time present of any movement over total time is also easy, allowing for inter-rater reliability.
- d. Because of its sensitivity, it is particularly important to monitor change.
- e. It can be performed in a very limited time. Usually we observe any passive and active movements during the clinical assessment and then ask the patient to read, write and move their limbs as needed.

However, the STRAW as a test is largely unknown, unfortunately not surprising, because though the scoring model was used in the initial study of high dose buspirone in tardive dyskinesia [71], proving extremely useful, it was not further marketed

and this is the first presentation at an International Conference [60]. However, the author of the STRAW, Dr Vernon Neppe has not published beyond this on the STRAW. This has continued despite thousands of patients being monitored by the STRAW for movement disorder and tardive dyskinesia. This is needed clinically because any patients on neuroleptics should be regularly monitored for movement disorder. The STRAW has proven an extremely useful evaluation technique at different severity levels of tardive dyskinesia, and monitoring change. Given that we have never seen a patient tolerating high dose buspirone given in adequate frequency and with the dosage tailored for the patient who has not improved significantly, we recognize the enormous importance of adequate monitoring.

On the other hand, the STRAW does not specifically examine for reflexes such as glabella tap and salivation as in the Simpson-Angus and sometimes in variations of the AIMS. It was never meant as an all encompassing movement disorder scale, and should be used at least in conjunction with the AIMS variation above. The anatomical variations were adapted from the SCT HANS, but this was modified by Neppe so it also uses a 0-10 scale. The original SCT HANS did not. This is the reason why other scales are also used clinically besides the research comparison values. The SCT. Hans Rating Scale (SHRS) is a more multidimensional rating scale for the evaluation of neuroleptic-induced hyperkinesia, parkinsonism, akathisia and dystonia, whereas the focus of the STRAW is tardive dyskinesia.

Which scales are used the most? [72]

In one study, the Simpson-Angus Scale was used the most,

followed by one we've not detailed, the Extrapyramidal Symptom Rating Scale. There is still limited psychometric data, especially regarding validity, available for any scale: The Simpson-Angus Scale, the Drug-Induced Extrapyramidal Scale, and the parkinsonism subscale of the Schedule for the Assessment of Drug-Induced Movement Disorders (identical to the unmodified SCT Hans Rating Scale for Extrapyramidal Syndromes) appear to have moderate to good reliability and acceptable validity.

However, the time-consuming nature of the Schedule for the Assessment of Drug-Induced Movement Disorders would make it less useful in daily practice. This is why the STRAW has set up a quick way to use the positives of the SCT Hans: The STRAW involves ensuring that all areas of the trunk and limbs are examined but this is by observation during an appointment. Whereas early on more than one rater examined the same patients with excellent inter-rater reliability, formal studies involving repeating video monitoring and re-evaluation and a cohort of several simultaneous or sequential raters on the same patient has not been done. So whereas it is straight forward, the formal inter-rater reliability has not been established.

This makes the STRAW a wonderful research project for proper standardization of inter-rater and intra-rater reliability with videos and several assessors [6].

References

- Crane GE (1968) Tardive dyskinesia in patients treated with major neuroleptics: a review of the literature. *Am J Psychiatry* 124(8): 40-48.
- Crane GE (1971) Package inserts and tardive dyskinesia. *Am J Psychiatry* 128(6): 783.
- Kovacic B, Domino EF (1982) A monkey model of tardive dyskinesia (TD): evidence that reversible TD may turn into irreversible TD. *J Clin Psychopharmacol* 2(5): 305-307.
- Leblhuber F, Reisecker F, Bengesser G (1987) Tiapride in the treatment of irreversible tardive dyskinesia--initial experiences. *Z Gerontol* 20(1): 49-51.
- Bourgeois M, Boueilh P, Tignol J (1980) Spontaneous dyskinesia in the elderly and tardive dyskinesia of neuroleptics. A survey among 270 patients (author's transl). *Encephale* 6(1): 37-39.
- Rimski B, Bokonjic N (1955) Clinical effect of largactil on dyskinesia]. *Med Arh* 9(5): 127-137.
- Tatlow WF, Fisher CM, Dobkin AB (1954) The clinical effects of chlorpromazine on dyskinesia. *Can Med Assoc J* 71(4): 380-381.
- Janssen P (1992) The "social chemistry" of pharmacological discovery: the haloperidol story. An interview with Dr. Paul Janssen, January 21, 1986. Interview by Stanley Einstein. *Int J Addict* 27(3): 331-346.
- Granger B (1999) The discovery of haloperidol. *Encephale* 25(1): 59-66.
- Gilbert MM (1969) Haloperidol in severe facial dyskinesia. Case report. *Dis Nerv Syst* 30(7): 481-482.
- Bateman DN, Dutta DK, McClelland HA, et al. (1979) Metoclopramide and haloperidol in tardive dyskinesia. *Br J Psychiatry* 135(6): 505-508.
- Kulkarni SK, Naidu PS (2001) Tardive dyskinesia: An update. *Drugs Today* 37(2): 97-119.
- Collaborators (2015) Package insert metoclopramide.
- American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders. Washington, USA.
- Neppe VM (2014) Clinical applications of the STRAW measures of severity and frequency of involuntary movements examination in tardive dyskinesia and movement disorders,. *The Journal of Neuropsychiatry and clinical neurosciences*, p. 19.
- Neppe VM (1989) High-dose buspirone in case of tardive dyskinesia. *Lancet* 2(8677): 1458.
- Cervera R, Asherson RA, Font J, et al. (1997) Chorea in the antiphospholipid syndrome. Clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. *Medicine* 76(3): 203-212.
- Neppe VM, Wessels WH (1979) Psychotic toleration of neuroleptic medication. *S Afr Med J* 56(27): 1979.
- Neppe VM (1989) Psychopharmacological strategies in non-responsive psychotics, in *Innovative Psychopharmacotherapy*. In: Neppe VM (Ed.), Raven press, New York, USA, pp. 94-122.
- Neppe VM (1990) Discussion: Carbamazepine in the non affective psychotic and non psychotic dyscontrol, in *Carbamazepine and ox-carbazepine in Psychiatry*. *International Clinical Psychopharmacology* 5(1): 55-58.
- Neppe VM (1990) Carbamazepine in the non affective psychotic and non psychotic dyscontrol. in *Carbamazepine and ox-carbazepine in psychiatry*. *International Clinical Psychopharmacology* 5(1): 43-54.
- Neppe VM (1990) *Innovative Psychopharmacotherapy*. (1st edn), Raven press, New York, USA.
- Neppe VM (1999) *Cry the beloved mind: a voyage of hope*. Brainquest Press, Washington USA.
- Harris MJ, Panton D, Caligiuri MP, et al. (1992) High incidence of tardive dyskinesia in older outpatients on low doses of neuroleptics. *Psychopharmacol Bull* 28(1): 87-92.
- Rosenheck RA, Davis VG, Davis SM, et al. (2009) Can a nonequivalent choice of dosing regimen bias the results of flexible dose double blind trials? The CATIE schizophrenia trial. *Schizophr Res* 113(1): 12-18.
- Egan MF, Hyde TM, Kleinman JE, et al. (1995) Neuroleptic-induced vacuous chewing movements in rodents: incidence and effects of long-term increases in haloperidol dose. *Psychopharmacology* 117(1): 74-81.
- Gao XM, Cooper T, Suckow RF, et al. (2006) Multidose risperidone treatment evaluated in a rodent model of tardive dyskinesia. *Neuropsychopharmacology* 31(9): 1864-1868.
- Kinon BJ, Jeste DV, Kollack WS, et al. (2004) Olanzapine treatment for tardive dyskinesia in schizophrenia patients: a prospective clinical trial with patients randomized to blinded dose reduction periods. *Prog Neuropsychopharmacol Biol Psychiatry* 28(6): 985-996.
- Yesavage JA, Bourgeois M, Kraemer H, et al. (1982) Prevalence of tardive dyskinesia in 3140 French inpatients. *J Nerv Ment Dis* 170(2): 111-112.
- Ertugrul A, Meltzer HY (2003) Antipsychotic drugs in bipolar disorder. *Int J Neuropsychopharmacol* 6(3): 277-284.

31. Casey DE (1999) Tardive dyskinesia and atypical antipsychotic drugs. *Schizophr Res* 35: 61-66.
32. Caroff SN, Mann SC, Campbell EC, et al. (2002) Movement disorders associated with atypical antipsychotic drugs. *J Clin Psychiatry* 63(4): 12-19.
33. Association. TfoTDotAP: The Task Force on Late Neurological Effects of Antipsychotic Drugs.
34. Tardive Dyskinesia Summary of a Task Force Report of The American Psychiatric Association. *Am J Psychiatr* 10: 137-140.
35. Amadio PB, Cross LB, Amadio P (1997) New drugs for schizophrenia: an update for family physicians. *Am Fam Physician* 56(4): 1149-1156.
36. Albers LJ, Ozdemir V (2004) Pharmacogenomic-guided rational therapeutic drug monitoring: conceptual framework and application platforms for atypical antipsychotics. *Curr Med Chem* 11(3): 297-312.
37. Anonymous (2005) Aripiprazole: new drug. Just another neuroleptic. *Prescrire Int* 14(79): 163-167.
38. Adam UU, Husain N, Haddad PM, et al. (2014) Tardive dyskinesia in a South Asian population with first episode psychosis treated with antipsychotics. *Neuropsychiatr Dis Treat* 10: 1953-1959.
39. Janno S, Holi MM, Tuisku K, et al. (2008) Neuroleptic-induced movement disorders in a naturalistic schizophrenia population: diagnostic value of actometric movement patterns. *BMC Neurol* 8: 10.
40. Sprague RL, Kalachnik JE (1991) Reliability, validity, and a total score cutoff for the dyskinesia identification system: condensed user scale (DISCUS) with mentally ill and mentally retarded populations. *Psychopharmacol Bull* 27(1): 51-58.
41. Glick ID, Murray SR, Vasudevan P, et al. (2001) Treatment with atypical antipsychotics: new indications and new populations. *J Psychiatr Res* 35(3): 187-191.
42. Muscettola G, Barbato G, Pampallona S, et al. (1999) Extrapyramidal syndromes in neuroleptic-treated patients: prevalence, risk factors, and association with tardive dyskinesia. *J Clin Psychopharmacol* 19(3): 203-208.
43. Morgenstern H, Glazer WM (1993) Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with neuroleptic medications. Results of the Yale Tardive Dyskinesia Study. *Arch Gen Psychiatry* 50(9): 723-733.
44. Bailey LG, Maxwell S, Brandabur MM (1997) Substance abuse as a risk factor for tardive dyskinesia: a retrospective analysis of 1,027 patients. *Psychopharmacol Bull* 33(1): 177-181.
45. Sewell DD, Yoshinobu BH, Caligiuri MP, et al. (1992) Metoclopramide-associated tardive dyskinesia in hemodialysis patients with diabetes mellitus. Two case reports. *Gen Hosp Psychiatry* 14(6): 416-419.
46. Ganzini L, Casey DE, Hoffman WF, et al. (1992) Tardive dyskinesia and diabetes mellitus. *Psychopharmacol Bull* 28(3): 281-286.
47. Orme ML, Tallis RC (1984) Metoclopramide and tardive dyskinesia in the elderly. *Br Med J* 289(6442): 397-398.
48. O'Brien J, Barber R (1998) Marked improvement in tardive dyskinesia following treatment with olanzapine in an elderly subject. *Br J Psychiatry* 172: 186.
49. Madhusoodanan S, Brenner R, Gupta S, et al. (2004) Clinical experience with aripiprazole treatment in ten elderly patients with schizophrenia or schizoaffective disorder: retrospective case studies. *CNS Spectr* 9(11): 862-867.
50. Kirkwood CK, Givone DM (2003) Advances in pharmacotherapy of psychotic disorders in the elderly. *Consult Pharm* 18(6): 539-550.
51. Jeste DV, Rockwell E, Harris MJ, et al. (1999) Conventional vs. newer antipsychotics in elderly patients. *Am J Geriatr Psychiatry* 7(1): 70-76.
52. Jenike MA (1989) Treatment of affective illness in the elderly with drugs and electroconvulsive therapy. *J Geriatr Psychiatry* 22(1): 77-112.
53. Caligiuri MR, Jeste DV, Lacro JP (2000) Antipsychotic-Induced movement disorders in the elderly: epidemiology and treatment recommendations. *Drugs Aging* 17(5): 363-384.
54. Bullock R, Saharan A (2002) Atypical antipsychotics: experience and use in the elderly. *Int J Clin Pract* 56(7): 515-525.
55. Anonymous (1992) Metoclopramide: an analysis of inappropriate long-term use in the elderly. *Ann Pharmacother* 26(7-8): 977-979.
56. Archer T (1993) Behavioural retardation in the neuropathology of mental retardation. *APMIS* 40: 35-56.
57. Fischer P, Tauscher J, Kufferle B (1998) Risperidone and tardive dyskinesia in organic psychosis. *Pharmacopsychiatry* 31(2): 70-71.
58. Miller LG, Jankovic J (1990) Neurologic approach to drug-induced movement disorders: a study of 125 patients. *South Med J* 83(5): 525-532.
59. Tiwari AK, Deshpande SN, Lerer B, et al. (2006) Genetic susceptibility to Tardive Dyskinesia in chronic schizophrenia subjects: V. Association of CYP1A2 1545 C>T polymorphism. *The Pharmacogenomics Journal*, pp. 305-311.
60. Neppe VM (1990) Ethics and informed consent for double-blind studies on the acute psychotic. *Medical Psychiatric Correspondence. A Peer Reviewed Journal* 1(1): 44-45.
61. Burti L, Parolin A, Zanotelli R (1981) Tardive dyskinesia. AIMS (Abnormal Involuntary Movement Scale) as a diagnostic and research tool. *Minerva Med* 72(42): 2829-2836.
62. Anonymous (1988) Abnormal Involuntary Movement Scale (AIMS). *Psychopharmacol Bull* 24(4): 781-783.
63. Gharabawi GM, Bossie CA, Lasser RA, et al. (2005) Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia. *Schizophr Res* 77(2-3): 119-128.
64. Krausz M, Moritz SH, Naber D, et al. (1999) Neuroleptic-induced extrapyramidal symptoms are accompanied by cognitive dysfunction in schizophrenia. *Eur Psychiatry* 14(2): 84-88.
65. Goff DC, Midha KK, Brotman AW, et al. (1991) An open trial of buspirone added to neuroleptics in schizophrenic patients. *J Clin Psychopharmacol* 11(3): 193-197.
66. Neppe VM (2014) Tardive dyskinesia revisited: A voyage into high dose buspirone management-a clinical priority perspective.
67. Neppe VM (2014) Clinical applications of the STRAW measures of severity and frequency of involuntary movements examination in tardive dyskinesia and movement disorders. *J Neuropsychiatry and Clinical Neurosciences* 26(2): 2014.
68. Neppe VM (1999) Curing the incurable, in *Cry the Beloved Mind: A*

- Voyage of Hope. Brainquest Press, Washington, USA, pp. 311-343.
69. Neppe VM (1989) High-dose buspirone in case of tardive dyskinesia. *Lancet* 334(8677): 1458.
 70. Gerlach J, Korsgaard S, Clemmesen P, et al. (1993) The St. Hans Rating Scale for extrapyramidal syndromes: reliability and validity. *Acta Psychiatr Scand* 87(4): 244-252.
 71. Neppe VM (1989) The clinical neuropharmacology of buspirone, in *Innovative Psychopharmacotherapy*. In: Neppe VM (Ed.), Raven press, New York, USA, p. 35.
 72. Knol W, Keijsers CJ, Jansen PA, et al. (2010) Systematic evaluation of rating scales for drug-induced parkinsonism and recommendations for future research. *J Clin Psychopharmacol* 30(1): 57-63.