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Chapter 25

The psychopharmacology of catatonia, neuroleptic malignant syndrome, akathisia, tardive dyskinesia, and dystonia

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Abstract

Although highly prevalent, motor syndromes in psychiatry and motor side effects of psychopharmacologic agents remain understudied. Catatonia is a syndrome with specific motor abnormalities that can be seen in the context of a variety of psychiatric and somatic conditions. The neuroleptic malignant syndrome is a lethal variant, induced by antipsychotic drugs. Therefore, antipsychotics should be used with caution in the presence of catatonic signs. Antipsychotics and other dopamine-antagonist drugs can also cause motor side effects such as akathisia, (tardive) dyskinesia, and dystonia. These syndromes share a debilitating impact on the functioning and well-being of patients. To reduce the risk of inducing these side effects, a balanced and well-advised prescription of antipsychotics is of utmost importance. Clinicians should be able to recognize motor side effects and be knowledgeable of the different treatment modalities.

INTRODUCTION

Motor symptoms can be seen in psychiatric practice as an early symptom (e.g., mild dyskinesia in patients at risk for psychosis), a separate syndrome (such as catatonia), or a side effect of predominantly dopamine blocking agents, mainly antipsychotics. Although highly prevalent, these motor syndromes and side effects of psychopharmacologic agents remain understudied. With an increasing number of patients using antipsychotics for various indications, the absolute number of patients experiencing motor side effects is not expected to decrease. A systematic screening for motor symptoms should be part of a routine psychiatric examination, given their high prevalence. A number of rating scales and screening instruments are available, and can be used to guide the clinician in the diagnostic process. It has been shown, for example, that the use of a rating scale increases the likelihood of diagnosing a catatonic syndrome (van der Heijden et al., 2005).

In this chapter a brief overview is provided of catatonia, and its lethal variant, the neuroleptic malignant syndrome, akathisia, tardive dyskinesia, and dystonia. Some clinical characteristics are described, and, where available, recommended clinical interventions are discussed.

CATATONIA

Catatonia is a syndrome characterized by specific motor signs, such as catalepsy, rigidity, posturing, mannerisms, stereotypies, negativism, and automatic obedience, at times aggravated by autonomic dysfunction and fever (Dhossche et al., 2016). It has an acute onset and a fluctuating course. Catatonia can be life threatening but, if recognized early and treated adequately, has a good prognosis. Its estimated prevalence among psychiatric

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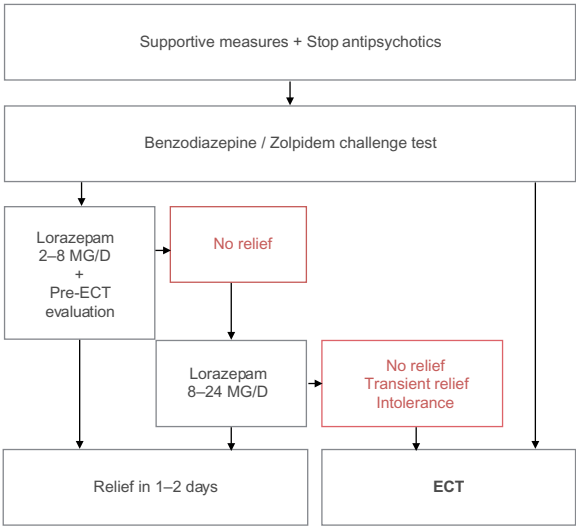

Fig. 25.1. Simplified treatment algorithm for catatonia.

inpatients is 10% (Pommepuy and Januel, 2002). One-third of catatonic patients suffer from schizophrenia, while an even larger proportion (43%) has a bipolar disorder (Rosebush and Mazurek, 2010). In up to 25% of cases, catatonia is related to general medical or neurologic conditions (Daniels, 2009; Oldham, 2018), such as anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis (Herken and Pruss, 2017).

A prompt recognition of catatonia is paramount to initiate treatment without delay (Pelzer et al., 2018). Catatonic symptoms wax and wane, and to diagnose catatonia symptoms should be observed on at least two separate occasions. Specific catatonic signs should be elicited during a neuropsychiatric examination. Such a clinical examination, guided by a screening instrument, such as the Bush Francis Catatonia Rating Scale (BFCRS), can be integrated easily in the routine neuropsychiatric examination (Sienaert et al., 2011). The etiology of catatonia remains elusive. The main hypotheses involve dopamine hypoactivity, an imbalance in the gamma-aminobutyric acid (GABA) transmission, and glutamate hyperactivity (Dhossche et al., 2010; Gazdag and Sienaert, 2013) (Fig. 25.1).

Treatment

Antipsychotics

Although some authors have advocated the use of antipsychotics in catatonia in schizophrenia (van den Eede et al., 2005), it is generally acknowledged that these drugs are not effective and, moreover, carry the risk of worsening the condition and inducing a malignant catatonia (Paparrigopoulos et al., 2009; Sienaert et al., 2014; Fink et al., 2016; Rasmussen et al., 2016). This unfavorable effect is especially associated with the use of first-generation antipsychotics (FGAs) (Sienaert et al., 2013). Several reports suggest a beneficial effect of clozapine and second-generation antipsychotics (SGAs) in the treatment of (chronic) schizophrenic catatonia. SGA with low D2 blockade (quetiapine, olanzapine, clozapine) (Tabbane et al., 2016) or with D2 partial agonism (aripiprazole) (Muneoka et al., 2017) should be favored, and can, of course, be used to treat residual psychotic symptomatology or as a prophylactic treatment in psychotic disorders and mood disorders (Sienaert et al., 2014).

Benzodiazepines

Benzodiazepine challenge

The vast majority of patients will show a quick and abrupt improvement of catatonic symptomatology after the administration of a benzodiazepine (Hawkins et al., 1995; Payee et al., 1999; Sienaert et al., 2014). The response is so dramatic, that it has become a diagnostic tool, called the *Lorazepam (or Zolpidem) Challenge Test*. After the patient is examined for signs of catatonia, 1 or 2 mg of lorazepam is administered intravenously (IV), intramuscularly (IM), or orally (PO). After 10, 15, or 30 min, respectively, the patient is reexamined. If there has been no change, a second dose is given, and the patient is again reassessed (Bush et al., 1996; Fink and Taylor, 2003). A marked reduction (e.g., at least 50%) of catatonic signs and symptoms, as measured with a standardized rating scale, confirms the diagnosis. As an alternative to lorazepam, zolpidem 10 mg PO can be used, with a reassessment after 30 min (Thomas et al., 1997).

Lorazepam

Although there is no evidence of the superiority of lorazepam over other benzodiazepines, it is the recognized first-line treatment for catatonia, with response rates between 67% and 86%, within hours (Sienaert et al., 2014; Rasmussen et al., 2016). If a patient responds adequately to the initial dose of 1–2 mg lorazepam, the same dose should be continued (e.g., 2 mg per day). If not, it should be repeated every 3–4 h. If catatonic symptoms do not subside, the dose should be increased up to 8–24 mg lorazepam per day using daily incremental dosages (Sienaert et al., 2014; Dhossche et al., 2016; Rasmussen et al., 2016). With an adequate dose, most patients achieve remission of catatonia within 3–7 days. There is no consensus on how long benzodiazepines are to be continued, and generally they are discontinued once the underlying illness has remitted. In a number of cases, however, catatonic symptoms will reemerge each time lorazepam is tapered off, urging the clinician to continue benzodiazepines for an extended period of time (Grover and Aggarwal, 2011). Interestingly, lorazepam seems to

be effective, regardless of the underlying condition, although catatonia in mood disorders responds more frequently (92%–97%) than catatonia in the context of medical conditions (82%) or schizophrenia (59%) (Sienaert et al., 2014).

Zolpidem

Zolpidem can be used as an alternative to lorazepam, as shown in a series of case reports and small open studies from a French research-group (Mastain et al., 1995; Rascle et al., 1997; Thomas et al., 1997). This beneficial response to zolpidem was confirmed by others (Peglow et al., 2013; Hlal et al., 2014). Doses ranging from 7.5 to 40 mg per day have been reported, without noticeable adverse effects, for the continuation treatment (Peglow et al., 2013; Hlal et al., 2014).

Lorazepam–diazepam

As yet another alternative, Huang et al. (2013) have proposed a lorazepam–diazepam protocol. If patients, after an initial 2 mg lorazepam IM, do not or only partially respond, after 2 h a second dose is administered. If this fails, an IV drip of 10 mg diazepam in 500 mL normal saline at a rate of 1.25 mg/h for 1 day is prescribed. Several studies have reported very impressive results. Of 12 patients with mood disorders, 8 patients had full remission of catatonia after one dose of 2 mg lorazepam IM. Two patients needed an additional dose of lorazepam, and two patients recovered using 10 mg diazepam IV over 8 h (Huang et al., 2013). In patients with schizophrenia with catatonia, 13 of 21 (62%) patients responded within 2 h, 18 (86%) responded within 1 day, and all became catatonia-free within a week (Lin and Huang, 2013). In a recent study, 18 (86%) of 21 patients with catatonia secondary to a general medical condition responded swiftly after the lorazepam–diazepam protocol (Lin et al., 2017). It should be noted that all publications on the successful use of this protocol are from the same research group.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) should be started without delay in a patient with catatonia who is not responding to benzodiazepines, when a rapid response is required in life-threatening conditions or when the underlying condition, e.g., psychotic depression, warrants ECT as a treatment of first choice (Sienaert et al., 2014; Fink et al., 2016). The excellent efficacy of ECT in catatonia is generally acknowledged, although randomized controlled evidence is virtually lacking. Girish and Gill randomized 14 inpatients with catatonic schizophrenia and nonresponsive to lorazepam to receive either sham ECT plus risperidone (4–6 mg/day) or ECT (bitemporal, 3/W) plus oral placebo. BFCRS scores reduced markedly in both groups, but the reduction was significantly more profound in the ECT group (Girish and Gill, 2003). In a study comparing bifrontal and bitemporal ECT (Puthane et al., 2012), a posthoc analysis showed that patients with catatonic schizophrenia ($N = 19$) responded faster to ECT than other schizophrenia-subtypes ($N = 34$), and needed on average 1 session less to achieve clinical improvement (Thirthalli et al., 2009).

A longer duration of untreated catatonia likely predicts a (s)lower treatment response (Raveendranathan et al., 2012; Bastiampillai and Mohan, 2017; Low et al., 2017). Possible predictors of a better outcome are younger age, the presence of autonomic dysregulation, a greater symptom severity, and an underlying mood disorder (as opposed to schizophrenia or neurologic disease) (Luchini et al., 2015). Experts stress the use of bitemporal electrode placement with age-based supra-threshold dosing (Sienaert et al., 2014; Fink et al., 2016), although several alternative forms of ECT-techniques (unilateral electrode placement, ultrabrief currents) have been reported to be successful.

If catatonia is severe, in febrile, dehydrated, and excited delirious patients, daily treatments should be offered (Fink et al., 2016). As in state-of-the-art ECT, a fixed number of treatments should not be prescribed, but ECT should be continued until complete remission.

Some authors have suggested that the combination of ECT and benzodiazepines might be synergistic, as opposed to this combination in other indications (Petrides et al., 1997). In a retrospective study of 57 catatonic patients (63.2% with mood disorders and 29.8% with psychotic disorders) the combination of benzodiazepines and ECT yielded a 100% full recovery rate (Unal et al., 2013). In clinical practice, benzodiazepines will often be used during the course of ECT, since rapid benzodiazepine withdrawal before or during ECT might provoke the reemergence of catatonic symptoms. This phenomenon has been described in several cases (Luchini et al., 2015).

Other pharmacologic treatments

There is anecdotal evidence and evidence from a case series to treat catatonia with *N*-methyl-D-aspartic acid antagonists—amantadine and its derivative memantine (Carroll et al., 2007)—and various other pharmacologic agents, such as bromocriptine, biperiden, valproate, levetiracetam, topiramate, and carbamazepine (Sienaert et al., 2014).

Resistant catatonia

There is no guidance for the clinician on how to proceed after benzodiazepines and ECT have failed. Based on

some case reports, the use of zolpidem (Mastain et al., 1995; Javelot et al., 2015; Amorim and McDade, 2016) or lorazepam in a very high dosage (28 mg/day) (van der Markt et al., 2015) is advised. Based on pathophysiology, several hypothetical approaches have been proposed, such as oxytocin (because of its impact on fear and anxiety as it acts on the amygdala) (Ellul and Choucha, 2015) or GABAergic-glutamatergic drugs such as acamprosate and lamotrigine (Ellul and Choucha, 2015).

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome (NMS) is considered by several authors to be a drug-induced form of catatonia accompanied by fever and autonomic abnormalities, with mortality rates as high as 10% (Strawn et al., 2007), due to renal failure, cardiorespiratory arrest, disseminated intravascular coagulation, pulmonary emboli, or aspiration pneumonia. It is virtually impossible to differentiate NMS from malignant or lethal catatonia, and treatment is largely similar. Both NMS and lethal catatonia represent a spectrum with similar underlying pathophysiologic processes.

The current criteria for diagnosis of NMS are very similar to the first description by Delay and colleagues in 1960 (Delay et al., 1960), shortly after the introduction of antipsychotics. Its prominent features are rigidity, autonomic dysfunction, fever, and stupor. Laboratory alterations, e.g., leukocytosis and creatine kinase (CK) elevations (median CK elevations 800–1000 IU/L), metabolic acidosis, and low serum iron levels may be present (Caroff et al., 2011; Oruch et al., 2017).

The incidence has dropped from 3% to an estimate of 0.01%–0.02% (Strawn et al., 2007), most probably due to the introduction of SGA and the greater awareness and, hence, more conservative prescription of antipsychotics. NMS is more often seen at a younger age (20–25 years) and patients are 50% more likely to be male (Gurrera, 2017). About 16% of cases develop within 24 h and two-thirds occur during the first 1–2 weeks after the initiation of an antipsychotic (Caroff et al., 2011). High-potency antipsychotics, rapid titration, or oily long-acting depot forms of antipsychotics may increase the risk of NMS (Oruch et al., 2017). NMS is associated with virtually all antipsychotics, including SGAs. SGAs are, however, less prone to induce NMS, and SGA-induced NMS is less severe and has a lower mortality (Trollor et al., 2012; Belvederi Murri et al., 2015). NMS can also be triggered by withdrawal of dopaminergic agents (e.g., amantadine, L-Dopa), by antidopaminergic drugs (e.g., metoclopramide) or drugs with unestablished antidopaminergic action (e.g., lithium salts or valproate) (Oruch et al., 2017).

The predominant pathophysiologic process underlying NMS entails hypothalamic dopamine receptor blockade resulting in autonomic dysregulation. However, reduced GABA-inhibition of the frontal corticostriatal tracts may also be involved, illustrated by the fact that GABA-a-agonists have been shown to alleviate NMS (Carroll, 2000). Hence, NMS can be described as a complex cascade of neurochemical and neuroendocrine dysregulations, triggered by a reduction of dopaminergic tone and autonomic dysregulation, culminating in an end-stage hypermetabolic state (Belvederi Murri et al., 2015).

Treatment

Considering the potentially lethal course, treatment should be prompt and includes admission to an intensive care unit for circulatory and ventilatory support, cooling (in case of hyperthermia), fluid and electrolyte balance monitoring, and decubitus ulcer prevention and infection prevention (Oruch et al., 2017). The causative (dopamine-blocking) agent should be discontinued without delay. This resolves two-thirds of cases within 1–2 weeks (Caroff et al., 2011). Pharmacologic treatment can be used for symptomatic treatment of the complications. A clear consensus on the treatment of NMS is lacking (Oruch et al., 2017). Randomized-controlled trials (RCTs) are absent, and difficult to conduct, considering the low incidence. Clinical reports advocate the use of benzodiazepines, dopamine agonists, dantrolene, and ECT. Strawn et al. (2007) have provided a clear overview of putative beneficial interventions.

Benzodiazepines

As in catatonia, benzodiazepines may be used to reduce muscle rigidity and agitation. Some authors have reported benzodiazepines ameliorate symptoms and hasten recovery, whereas others have reported only transient or no effects (Strawn et al., 2007). Given the limited risks of benzodiazepines, a trial with lorazepam (1–2 mg parenterally every 4–6 h), should be considered, especially in those cases in which the differentiation between malignant catatonia and NMS is unclear (Strawn et al., 2007).

Dopamine agonists

To reverse the hypothesized dopaminergic blockade, a dopamine agonist (e.g., bromocriptine, amantadine) may be beneficial. Bromocriptine is generally initiated at 2.5–5 mg PO, 2–3 times/day, with a maximum of 45 mg/day. Amantadine may be started in divided doses (100 mg PO, every 8 h). Notably, both bromocriptine and amantadine can induce hypotension and may increase psychotic symptoms.

Dantrolene

In case of severe NMS, with hyperpyrexia, rigidity and true hypermetabolism (including severe rigidity, coma, fever (≥40°C/104°F), and tachycardia (≥120 bpm)), dantrolene, a strong muscle relaxant, may ameliorate symptoms. Published results are, however, not unequivocal (Reulbach et al., 2007). In combination with other muscle relaxants or sedatives, such as benzodiazepines, the effect of the latter may increase. The use of calcium channel blockers is contraindicated since, in animal research, it was demonstrated that the combination of dantrolene and calcium channel blockers may provoke cardiovascular collapse. Dantrolene should be administered IV, with an initial dose of 1–2.5 mg/kg body weight. If necessary, administration should be continued with 1 mg/kg every 6 h until symptom resolution or until a cumulative dose of 10 mg/kg body weight has been reached (Strawn et al., 2007). After the first few days, IV administration can be replaced by oral administration. How long dantrolene should be continued is not clear, but premature discontinuation can result in a reemergence of symptoms.

ECT

As in catatonia, ECT is a very effective and life-saving treatment for NMS (Trollor and Sachdev, 1999), even in medication resistant cases and/or in the late course of NMS (Strawn et al., 2007). Some authors argue that "ECT is doubtless the conservative treatment of choice for (lethal catatonia) as well as its neuroleptic-induced twin" (Abrams, 2002). It is of note that there might be an increased risk of hyperkalemia on being exposed to succinylcholine—the relaxant of first choice in ECT—justifying the use of nondepolarizing relaxants. There is little evidence of an increased risk of malignant hyperthermia in NMS because of the substances used in anesthesia (Verdura Vizcaínoa et al., 2011).

After resolution of NMS, the need for the NMS-inducing agent should be reconsidered. If the clinical condition requires antipsychotic treatment, these can be restarted, after a period of least 2 weeks. SGA should be titrated with caution, starting at a low dose, and symptoms of NMS should be thoroughly assessed (Strawn et al., 2007; Oruch et al., 2017).

AKATHISIA

In 1901, Ladislav Haškovec, professor of neuropathology at the University of Prague, coined the term akathisia as a symptom of hysteria or neurasthenia. Although today it is considered a predominantly drug-induced phenomenon, it was not until the 1950s that akathisia was linked to neuroleptic drugs. In DSM-V, akathisia is defined as a movement disorder characterized by subjective but observable complaints of restlessness and excessive movements (fidgeting of legs, rocking from foot to foot, pacing, inability to sit or stand still) (American Psychiatric Association, 2013). Prevalence rates vary greatly, ranging from 4.6% to over 75% (Sachdev, 1995; Janno et al., 2004; Bakker et al., 2011) depending on the setting and measurements used. In general, it evolves within 2 weeks—but often within hours or days—after starting or increasing the dosage of dopamine-blocking agents. Despite greater awareness, akathisia is frequently misdiagnosed and under-treated, with detrimental consequences. First, akathisia decreases medication-adherence. In addition, it may be misinterpreted as a worsening of the underlying condition, leading to a neuroleptic dose increase, which will further exacerbate akathisia. Finally, suicidality has been associated with akathisia (Akagi and Kumar, 2002; Cheng et al., 2013), stressing the need for prompt recognition.

The clinical diagnosis of akathisia may be difficult, partly because the severity can vary according to the situation and a person's degree of arousal. It has to be differentiated from psychotic agitation and anxiety, drug abuse or withdrawal syndromes, some somatic illnesses (e.g., hyperthyroidism, hyponatremia), or neurologic disorders (e.g., Parkinson's disease, restless legs syndrome) (Miller and Fleischhacker, 2000; van Harten, 2002; Lohr et al., 2015). The Barnes Akathisia Rating Scale (BARS), a 4-item scale with good validity and reliability, is recommended to diagnose akathisia, as well as to monitor its severity.

Our understanding of the pathophysiology of akathisia remains limited. Its association with antidopaminergic agents supports the notion that it may be linked to antagonism of mesocortical and mesolimbic dopaminergic pathways. However, responses to anticholinergics and β-adrenergic blockers, and the occurrence of akathisia in newer, serotonin-acting antipsychotics (e.g., aripiprazole, asenapine, lurasidone) (Thomas et al., 2015) and during treatment with SSRI, which potentiate 5-HT neurotransmission, suggest a role for other neurotransmitters as well (Rathbone and Soares-Weiser, 2006; Caroff et al., 2011). It seems likely that a complex interplay of several neurotransmitter systems and brain circuits underlies the complex pathophysiology. In addition, findings on a genetic predisposition remain inconclusive, but future studies may shed light on the familial loading of extrapyramidal symptoms.

Akathisia can be provoked by a wide variety of agents, including antidepressants, neuroleptics, anti-emetics (e.g., metoclopramide), preoperative sedatives, calcium channel blockers, and antivertigo agents. The vast majority of akathisia, however, has been associated with antipsychotics. In particular antipsychotic polytherapy should

be considered with caution. In a community-dwelling sample of patients with schizophrenia, antipsychotic polytherapy was administered to 30.4% of the cases and entailed a threefold risk of akathisia, as compared to monotherapy (Berna et al., 2015). In general, SGAs are believed to provoke less extrapyramidal symptoms, including akathisia, as compared to FGAs (Kumar and Sachdev, 2009; Berna et al., 2015; Lohr et al., 2015).

Treatment

On diagnosis, the need for akathisia-inducing drugs should be carefully reviewed. Antipsychotic polytherapy should be avoided. If feasible, the causative agent should be tapered or stopped. FGA can be replaced by SGA. Clozapine is suggested as the first choice of SGA in patients with a history of akathisia (Spivak et al., 1997; Modestin et al., 2008; Oh et al., 2015). Recently, Ribeiro et al. (2018) suggested that aripiprazole may cause less akathisia than risperidone. The CATIE study, however, demonstrated that different SGAs did not differ in the relative risk of akathisia (Miller et al., 2008).

β-blockers

When dose reduction or discontinuation of the susceptible drug is impossible, adjuvant drug therapies can be considered. Based on available literature, lipophilic β-blockers (e.g., propranolol) may be useful. A Cochrane review, however, could not undisputedly demonstrate the efficacy of β-blockers for akathisia. Only three RCTs were identified, hampering firm conclusions (Lima et al., 2004). Low doses of propranolol are advised, e.g., 10 mg three times daily, which can be increased to 90–120 mg/day, depending on side effects. In general, the effect is visible within hours to days (Miller and Fleischhacker, 2000).

Benzodiazepines

The evidence for further treatment steps is limited. Benzodiazepines are used, due to their anxiolytic and sedative properties, but their efficacy is uncertain (Berna et al., 2015). Benzodiazepines with a longer half-life may be preferable. Lorazepam or clonazepam may be suitable for a trial in clinical practice. A trial with a benzodiazepine should be closely monitored and stopped when significant symptom improvement is not achieved. Long-term benzodiazepine use may not be advisable (Berna et al., 2015).

Anticholinergics

Anticholinergics (e.g., biperiden 2–6 mg/day) have been used, but are thought to be most effective in the presence of concomitant parkinsonism (Caroff et al., 2011). A Cochrane review concluded that there is no reliable evidence to support or refute the use of anticholinergics for people suffering from neuroleptic-induced acute akathisia (Rathbone and Soares-Weiser, 2006). A more recent study, albeit with a cross-sectional design, among community-dwelling persons with schizophrenia could also not demonstrate that anticholinergic drugs were associated with a lower risk of akathisia (Berna et al., 2015). In addition, especially in older persons, anticholinergic-acting agents may result in cognitive decline and should be prescribed with caution.

Antidepressants

Despite paucity of data, it was suggested that agents with marked serotonin 5-HT2A antagonism (e.g., mianserin and mirtazapine) may be efficacious for akathisia (Miller and Fleischhacker, 2000). In a meta-analysis, comprising only two studies of limited sample size ($n = 86$), efficacy of mirtazapine for the treatment of akathisia was demonstrated, with a Number Needed to Treat (NNT) of 4 for partial response and a NNT of 5 for complete remission (Praharaj et al., 2015). A recent Cochrane review showed that mirtazapine was associated with a clinically significant response on akathisia symptoms, but not on other extrapyramidal effects, but firm conclusions could not be drawn (Perry et al., 2018). Mirtazapine may be especially useful in persons who cannot tolerate β-blockers or in case of comorbid depression (Hieber et al., 2008). Hence, it was suggested that a trial of mirtazapine may be considered, if propranolol is not tolerated, contraindicated, or ineffective, but limitations in the evidence should be acknowledged (Pringsheim et al., 2018).

Amantadine, clonidine, piracetam, and valproic acid have been suggested, but evidence remains unsatisfactory (Miller and Fleischhacker, 2000; van Harten, 2002; Kane et al., 2009; Caroff et al., 2011).

To conclude, akathisia is a very burdensome drug-induced condition, characterized by both subjective complaints of restlessness and observable excessive movements. It is most frequently caused by antipsychotics, or other antidopaminergic agents, including antiemetics. Unfortunately, to date, convincing evidence for pharmacologic treatment, besides reduction or stopping the inducing agent, is lacking.

TARDIVE DYSKINESIA

Tardive dyskinesia (TD) is a severe side effect of long-term treatment with dopamine blocking agents. Its prevalence in patients on long-term treatment with FGA varies greatly depending on population characteristics, rating methods, and type of antipsychotic used and is

estimated to be around 25% (van Harten et al., 1996b, 2004; Bakker et al., 2011). SGAs reduce the risk, but the prevalence is still substantial (Correll and Schenk, 2008; Tenback et al., 2010). Several large, non-pharmaceutic company-sponsored trials did not find a difference between SGA and FGA in the incidence of TD (Lieberman et al., 2005; Casey, 2006; Jones et al., 2006; Kahn et al., 2008).

Antipsychotics, dyskinesia, and psychosis

Dyskinesia can either be a symptom of psychotic disorders, as is seen in antipsychotic naïve patients with a first psychotic episode and in individuals with an ultra-high risk (UHR) for psychosis, or a side effect of antipsychotics. The evidence showing that antipsychotics can induce TD is overwhelming, especially in the elderly. The one and three-year incidence of TD in elderly treated with FGAs is 26% and 60%, respectively (Jeste, 2000). Furthermore, a dopamine blocking antiemetic such as metoclopramide can also induce TD (Rao and Camilleri, 2010). It is of clinical importance that individuals with UHR and dyskinesia have a higher risk of developing a psychotic disorder, and antipsychotic naïve first episode psychotic patients with dyskinesia have a higher risk of cognitive impairment (Mittal et al., 2011; van Harten et al., 2014).

Clinical picture

Three clinically distinct variants of TD can be recognized. Eighty percent of cases present with the orofacial type characterized by the bucco–linguo–masticatory triad (Slotema et al., 2008). Limb–truncal dyskinesia consists of purposeless choreiform movements of trunk and/or limbs (van Harten et al., 1996b; Bakker et al., 2011). The often misdiagnosed respiratory dyskinesia is characterized by a fast *and* irregular breathing pattern, sometimes accompanied by gasping, sighing, grunting, forceful breathing, shortness of breath, and dyspnea (Muzyk et al., 2012). TD runs a chronic waxing and waning course (van Harten et al., 2006, 2008; Tenback et al., 2010; Bakker et al., 2011).

Pathophysiology

The two most common theories are the dopamine receptor supersensitivity and the neurotoxicity theory. They explain the development or increase of dyskinetic movements by supersensitivity or damage (by free radicals) of the dopamine receptor and a decrease of the dyskinetic movements when the antipsychotic dosage is increased, because of the blockade of supersensitive dopamine receptors. Several other hypotheses to explain TD have been proposed but go beyond the scope of this chapter (Margolese et al., 2005).

Treatment

Despite a stunning number of RCTs—over 500 studies have evaluated more than 90 different interventions—there is no evidence-based treatment for TD and guidelines are lacking (Soares-Weiser and Fernandez, 2007). Many methodological issues—short follow-up, small groups—hamper definite conclusions. To complicate matters further, the relationship between TD and antipsychotics is confounded by the relationship between dyskinesia and psychotic disorders as mentioned earlier. On the other hand, whether TD is a symptom or a side effect, treatment will influence both. Therefore, we propose a practical algorithm based on clinical practice and scientific evidence.

Prevention

Before initiating treatment with antipsychotics, the patient or the family should be informed about the risk of TD. This may help patients and family to recognize dyskinesia early. Clinicians should screen patients for motor symptoms systematically and repeatedly (e.g., every 6 months). Furthermore, knowledge of risk factors of TD is important. Three nontherapeutic risk factors were replicated: age, non-Caucasian ethnicity, and early drug induced extrapyramidal syndromes (Tenback et al., 2009; Tenback and van Harten, 2011; O'Brien, 2016). Other nonreplicated risk factors are tardive dystonia (van Harten et al., 1997, 2006), treatment nonresponse (Chakos et al., 1996), worse premorbid functioning (Strous et al., 2004) and intermittent antipsychotic treatment (van Harten et al., 1998). There is also a difference between the antipsychotics in their propensity to induce TD, with clozapine inducing almost none and quetiapine inducing less TD (Correll et al., 2004; Leucht et al., 2013).

Treatment

If a patient has TD, the need for antipsychotics should be reconsidered. Although many textbooks suggest lowering the antipsychotic dosage, there is not much evidence that this will decrease the severity of TD. Tapering antipsychotics should be weighed against the risk of a reemergence of symptoms of the psychiatric condition. The decision to start a treatment depends on the subjective distress and the objective disabilities caused by TD.

Antioxidants

Several antioxidants (free radical scavengers) that minimize the neurotoxic effect of free radicals have been studied: high doses of vitamin E, vitamin B6, melatonin, selegiline, Yi-gan san, *Ginkgo biloba* extract,

eicosapentaenoic acid, and a combination of vitamin E and C (Shi et al., 2016). The results are conflicting, and the effect is often limited. There is some evidence that vitamin E protects against deterioration of TD. Surprisingly, there is no study that addresses the preventive properties of vitamin E, e.g., in elderly patients starting with antipsychotics. Such a study would be of great clinical value.

Switch to clozapine

A meta-analysis including 16 studies showed that a switch to clozapine is very effective in reducing the severity of moderate to severe TD (Mentzel et al., 2018). Random-effects model showed that overall effect of switching to clozapine significantly reduces TD ($n_{patients} = 1060$, $d = -0.40$, $P < 0.01$). The effect was especially strong in the four studies that included patients with clinical levels of TD (i.e., moderate to severe) and had TD as a primary outcome ($n_{patients} = 48$, $d = -2.56$, $P = 0.02$) (Moore et al., 1992; Littrell and Magill, 1993; Spivak et al., 1997; Louza and Bassitt, 2005). Three of these four studies used the AIMS score to measure the severity of TD showing a mean reduction of 10.6 points (Moore et al., 1992; Littrell and Magill, 1993; Spivak et al., 1997).

Switch to another SGA

Only a few studies have addressed switching to an SGA or to an FGA or switching to a combination of SGA and FGA. A switch to the SGA quetiapine may reduce the severity of TD (Emsley et al., 2004; Cortese et al., 2008). One study reported comparable reduction of TD after a switch to the SGA olanzapine or risperidone (Chan et al., 2010). One very large observational study studied the persistence of TD after a switch to an SGA versus an FGA. Patients switching to an SGA showed less persistence of TD than those switching to an FGA (Tenback et al., 2010). In contrast, an 18-year prospective study including 223 patients with severe mental illness showed that switching from an FGA to an SGA did not result in a reduction of TD while adding an SGA to an FGA may reduce the severity of TD. Also starting/switching to an FGA reduced TD severity (Mentzel et al., 2017).

One study reported comparable reduction of TD after a switch to olanzapine or risperidone (Chan et al., 2010). One very large observational study studied the persistence of TD after a switch to SGA vs FGA. Patients switching to an SGA showed less persistence of TD than those switching to an FGA (Tenback et al., 2010).

Botulinum toxin

Botulinum toxin can be useful in focal severe TD, especially when accompanied by dystonic features. Several case reports show its effectiveness in orofacial dyskinesia complicated by tongue protrusion, which can be socially very disabling (van Harten and Hovestadt, 2006). A small single-blind study of 12 patients showed a nonsignificant reduction in the severity of orofacial dyskinesia (Slotema et al., 2008).

VMAT2 inhibitors

Tetrabenazine is a VMAT2 inhibitor that can be very effective in reducing TD, even after a short period of treatment. The risk of inducing depression (10%–15%) or parkinsonism, however, limits the use of this drug (Kenney et al., 2006). Deutetrabenazine has been studied in a placebo-controlled, randomized, double-blind, multicenter trial in 107 patients with moderate to severe TD. It significantly reduced the severity of TD. A depressed mood, as a side effect, was seen in 1.7% of the subjects (Fernandez et al., 2017). Valbenazine was recently approved for the treatment of TD, with a recommended dose of 80 mg/day (Scorr and Factor, 2018). In three RCTs, valbenazine was significantly better than placebo. In 40.0% of patients, TD severity was reduced by at least 50%, as opposed to 8.7% of patients in the placebo group, yielding a NNT of 4. Discontinuation rates were very low. Of note: valbenazine can prolong the QT interval (Citrome, 2017; Hauser et al., 2017; Touma and Scarff, 2018).

Deep brain stimulation

A review, based on case reports and small clinical trials, of deep brain stimulation (DBS) in patients with severe forms of TD, often combined with dystonia, showed remarkable improvement (mean improvement 78% on the Burke–Fahn–Marsden Dystonia Rating Scale) (Sako et al., 2011; Mentzel et al., 2012). Patients who were included in the trials had severe, often disabling TD and/or tardive dystonia and had tried clozapine and tetrabenazine without success. There were almost no psychiatric complications with DBS but acute psychiatric symptoms or severe depression, were exclusion criteria. The results suggest that bilateral globus pallidus stimulation may be a new treatment option for severe disabling TD.

DYSTONIA

Tardive dystonia is a side effect after long-term use of dopamine receptor antagonists, most often

antipsychotics. Although it is often classified as a variant of tardive dyskinesia, it can be defined as a separate syndrome based on different phenomenology, younger age at onset, lack of female predominance, and different reactions to anticholinergics. These drugs can alleviate tardive dystonia but may exacerbate tardive dyskinesia (Skidmore et al., 2005).

The following diagnostic criteria are suggested: (i) the patient must have dystonia, defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures, (ii) the dystonia must have developed either during or within 3 months of a course of a dopamine blocking agent (often antipsychotics), (iii) Wilson's disease must be ruled out and there must be no other neurologic signs to suggest one of the many causes of secondary dystonia, and (iv) there must be a negative family history for dystonia (Burke et al., 1982; Skidmore et al., 2005).

Half of the patients who will develop tardive dystonia do so within 5 years of exposure to antipsychotics (Burke et al., 1982). It can affect any area of the body; examples are torti-retro-laterocollis, blepharospasm, oromandibular, laryngeal, arm, trunk, and leg dystonia. The most common sites for tardive dystonia are the cranial and neck regions and the arms.

Tardive dystonia can be divided into focal (single body part affected), segmental (two or more contiguous body parts), multifocal (two or more noncontiguous body parts), and generalized (combined involvement of at least one leg and trunk and any other body part).

"Sensory tricks" are a specific feature of dystonia, present in about half of the patients (Svetel et al., 2004). Sensory tricks are tactile or proprioceptive stimuli that can remarkably relieve the severity or the subjective discomfort of the dystonia, e.g., touching the eyebrow to reduce blepharospasms.

The prevalence of tardive dystonia is about 5%, and is lower than that of tardive dyskinesia (van Harten and Kahn, 1999; Ryu et al., 2015). The only incidence study to date was done in a population who used antipsychotics for many years. The low incidence found (0.7%), in combination with the relatively high prevalence at baseline (13%), is in line with the idea that tardive dystonia most often begins in the first years of treatment (van Harten et al., 2006). This cohort was followed over 9 years and of the 26 patients with tardive dystonia at baseline most recovered (64%), but 20% persisted. The severity of dystonia at baseline predicted the persistence of tardive dystonia (van Harten et al., 2008). There are some risk factors suggested for tardive dystonia such as younger age, having tardive dyskinesia, history of acute dystonia, or being male (van Harten and Kahn, 1999).

Treatment

In a patient presenting with tardive dystonia, the necessity of antipsychotic treatment should be reassessed. In general, FGA should be avoided. It is of note, however, that these drugs also have the ability to suppress dystonia. Therefore, they have been used in patients with severe (generalized) tardive dystonia that is painful or causes muscle damage (based on elevated serum CPK) (Skidmore et al., 2005).

Switch to clozapine

A switch to clozapine can be very effective and many case reports and small studies underline its efficacy (van Harten et al., 1996a; Joe et al., 2015; Pinninti et al., 2015). As an alternative, olanzapine and quetiapine can be tried (Gourzis et al., 2015; Pinninti et al., 2015). Adding a benzodiazepine, in particular clonazepam, may increase the effect of a switch to clozapine. However, sedation may limit the use of this combination.

Botulinum toxin

In focal or segmental forms of tardive dystonia, botulinum toxin is often indicated. The paralytic effect of botulinum toxin subsides over a period of 2–3 months and reinjecting the muscles restores the original effect. According to several controlled clinical trials botulinum toxin is the treatment of choice in primary focal dystonias such as blepharospasm, cervical dystonia, oromandibular dystonia, laryngeal dystonia, and these findings can be extrapolated to tardive dystonia (Tarsy et al., 1997; Zoons et al., 2012).

VMAT2 inhibitors

As in tardive dyskinesia, VMAT2 inhibitors can also be of use for the treatment of tardive dystonia (see earlier text).

Anticholinergics

Whereas in acute dystonia, anticholinergics are extremely effective in normal doses, in tardive dystonia much higher doses are needed and the results are less impressive. An average dose of 20 mg trihexiphenidyl per day was effective, but such doses may induce severe side effects such as memory disturbances, confusion, and delirium, especially in the elderly (Skidmore et al., 2005).

Anticholinergics may relieve dystonia but increase dyskinesia.

Deep brain stimulation

The evidence for the use of DBS for primary dystonia is convincing, and several studies and case reports strongly suggest that these results can be extrapolated to medication refractory tardive dystonia. Medication refractory primary dystonia is thus seen as an indication for DBS (Speelman et al., 2010). The treatment is well tolerated, and one study showed significant improvement in psychiatric symptoms (Deng et al., 2017).

In conclusion, TD is an underestimated side effect of dopamine blocking agents. With an increasing number of patients using antipsychotics for various indications, the absolute number of patients is expected to rise. Prevention may be essential to reduce the risk and several treatment options have been suggested, based on evidence and clinical practice.

CONCLUSION

Clinicians should be able to recognize motor syndromes and motor side effects of psychopharmacologic drugs. A systematic screening for motor symptoms should be part of a routine psychiatric examination. In order to reduce the risk of inducing debilitating side effects, a balanced and well-advised prescription of antipsychotics is of utmost importance. Although the scientific evidence for most treatment suggested in the literature is limited, and clear guidelines are lacking, various interventions are available and should be explored to reduce the burden in the patients.

References

Abrams R (2002). Electroconvulsive therapy, Oxford University Press, Oxford, NY.

Akagi H, Kumar TM (2002). Lesson of the week: akathisia: overlooked at a cost. BMJ 324: 1506–1507.

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders, fifth ed. American Psychiatric Association, Arlington.

Amorim E, McDade EM (2016). Rapidly-progressive catatonia responsive to zolpidem in a patient with ovarian teratoma-associated paraneoplastic encephalitis. J Clin Neurosci 30: 136–138.

Bakker PR, De Groot IW, van Os J et al. (2011). Long-stay psychiatric patients: a prospective study revealing persistent antipsychotic-induced movement disorder. PLoS One 6. e25588.

Bastiampillai T, Mohan T (2017). Delayed ECT and catatonia prognosis. Asian J Psychiatr 25: 251–252.

Belvederi Murri M, Guaglianone A, Bugliani M et al. (2015). Second-generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis. Drugs R&D 15: 45–62.

Berna F, Misdrahi D, Boyer L et al. (2015). Akathisia: prevalence and risk factors in a community-dwelling sample of patients with schizophrenia. Results from the FACE-SZ dataset. Schizophr Res 169: 255–261.

Burke RE, Fahn S, Jankovic J et al. (1982). Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. Neurology 32: 1335–1346.

Bush G, Fink M, Petrides G et al. (1996). Catatonia. II. Treatment with lorazepam and electroconvulsive therapy. Acta Psychiatr Scand 93: 137–143.

Caroff SN, Hurford I, Lybrand J et al. (2011). Movement disorders induced by antipsychotic drugs: implications of the CATIE schizophrenia trial. Neurol Clin 29: 127–148. viii.

Carroll BT (2000). The universal field hypothesis of catatonia and neuroleptic malignant syndrome. CNS Spectr 5: 26–33.

Carroll BT, Goforth HW, Thomas C et al. (2007). Review of adjunctive glutamate antagonist therapy in the treatment of catatonic syndromes. J Neuropsychiatry Clin Neurosci 19: 406–412.

Casey DE (2006). Implications of the CATIE trial on treatment: extrapyramidal symptoms. CNS Spectr 11: 25–31.

Chakos MH, Alvir JM, Woerner MG et al. (1996). Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. Arch Gen Psychiatry 53: 313–319.

Chan HY, Chiang SC, Chang CJ et al. (2010). A randomized controlled trial of risperidone and olanzapine for schizophrenic patients with neuroleptic-induced tardive dyskinesia. J Clin Psychiatry 71: 1226–1233.

Cheng HM, Park JH, Hernstadt D (2013). Akathisia: a life-threatening side effect of a common medication. BMJ Case Rep 2013. https://doi.org/10.1136/bcr-2012-007713.

Citrome L (2017). Valbenazine for tardive dyskinesia: a systematic review of the efficacy and safety profile for this newly approved novel medication-what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract. 71 (7). https://doi.org/10.1111/ijcp.12964. (Epub 2017 May 12).

Correll CU, Schenk EM (2008). Tardive dyskinesia and new antipsychotics. Curr Opin Psychiatry 21: 151–156.

Correll CU, Leucht S, Kane JM (2004). Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 161: 414–425.

Cortese L, Caligiuri MP, Williams R et al. (2008). Reduction in neuroleptic-induced movement disorders after a switch to quetiapine in patients with schizophrenia. J Clin Psychopharmacol 28: 69–73.

Daniels J (2009). Catatonia: clinical aspects and neurobiological correlates. J Neuropsychiatry Clin Neurosci 21: 371–380.

Delay J, Pichot P, Lemperiere T et al. (1960). A non-phenothiazine and non-reserpine major neuroleptic, haloperidol, in the treatment of psychoses. Ann Med Psychol 118(1): 145–152.

Deng ZD, Li DY, Zhang CC et al. (2017). Long-term follow-up of bilateral subthalamic deep brain stimulation for refractory tardive dystonia. Parkinsonism Relat Disord 41: 58–65.

Dhossche DM, Stoppelbein L, Rout UK (2010). Etiopathogenesis of catatonia: generalizations and working hypotheses. J ECT 26: 253–258.

Dhossche DM, Wachtel LE, Goetz M et al. (2016). Catatonia in psychiatric illnesses. In: SH Fatemi, PJ Clayton (Eds.), The medical basis of psychiatry, Springer, New York.

Ellul P, Choucha W (2015). Neurobiological approach of catatonia and treatment perspectives. Front Psych 6: 182.

Emsley R, Turner HJ, Schronen J et al. (2004). A single-blind, randomized trial comparing quetiapine and haloperidol in the treatment of tardive dyskinesia. J Clin Psychiatry 65: 696–701.

Fernandez HH, Factor SA, Hauser RA et al. (2017). Randomized controlled trial of deutetrabenazine for tardive dyskinesia: the ARM-TD study. Neurology 88: 2003–2010.

Fink M, Taylor MA (2003). Catatonia: a clinician's guide to diagnosis and treatment, Cambridge, Cambridge University Press, New York.

Fink M, Kellner CH, McCall WV (2016). Optimizing ECT technique in treating catatonia. J ECT 32: 149–150.

Gazdag G, Sienaert P (2013). Diagnosing and treating catatonia: an update. Curr Psychiatr Rev 9: 130–135.

Girish K, Gill NS (2003). Electroconvulsive therapy in lorazepam non-responsive catatonia. Indian J Psychiatry 45: 21–25.

Gourzis P, Skokou M, Soubasi E et al. (2015). Treatment of tardive dystonia induced by antipsychotics, old and new. Clin Neuropharmacol 38: 121–126.

Grover S, Aggarwal M (2011). Long-term maintenance lorazepam for catatonia: a case report. Gen Hosp Psychiatry 33: 82. e1–3.

Gurrera RJ (2017). A systematic review of sex and age factors in neuroleptic malignant syndrome diagnosis frequency. Acta Psychiatr Scand 135: 398–408.

Hauser RA, Factor SA, Marder SR et al. (2017). KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of Valbenazine for tardive dyskinesia. Am J Psychiatry 174: 476–484.

Hawkins JM, Archer KJ, Strakowski SM et al. (1995). Somatic treatment of catatonia. Int J Psychiatry Med 25: 345–369.

Herken J, Pruss H (2017). Red flags: clinical signs for identifying autoimmune encephalitis in psychiatric patients. Front Psych 8: 25.

Hieber R, Dellenbaugh T, Nelson LA (2008). Role of mirtazapine in the treatment of antipsychotic-induced akathisia. Ann Pharmacother 42: 841–846.

Hlal H, Kettani N, Berhili N et al. (2014). Place du zolpidem dans le traitement des catatonies résistantes aux benzodiazépines. À propos d'un cas. Presse Med 43 (9): 1018–1020.

Huang YC, Lin CC, Hung YY et al. (2013). Rapid relief of catatonia in mood disorder by lorazepam and diazepam. Biomed J 36: 35–39.

Janno S, Holi M, Tuisku K et al. (2004). Prevalence of neuroleptic-induced movement disorders in chronic schizophrenia inpatients. Am J Psychiatry 161: 160–163.

Javelot H, Michel B, Steiner R et al. (2015). Zolpidem test and catatonia. J Clin Pharm Ther 40 (6): 699–701.

Jeste DV (2000). Tardive dyskinesia in older patients. J Clin Psychiatry 61 (Suppl. 4): 27–32.

Joe S, Park J, Lim J et al. (2015). Remission of irreversible aripiprazole-induced tardive dystonia with clozapine: a case report. BMC Psychiatry 15: 253.

Jones PB, Barnes TR, Davies L et al. (2006). Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). Arch Gen Psychiatry 63: 1079–1087.

Kahn RS, Fleischhacker WW, Boter H et al. (2008). Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 371: 1085–1097.

Kane JM, Fleischhacker WW, Hansen L et al. (2009). Akathisia: an updated review focusing on second-generation antipsychotics. J Clin Psychiatry 70: 627–643.

Kenney C, Hunter C, Mejia N et al. (2006). Is history of depression a contraindication to treatment with tetrabenazine? Clin Neuropharmacol 29: 259–264.

Kumar R, Sachdev PS (2009). Akathisia and second-generation antipsychotic drugs. Curr Opin Psychiatry 22: 293–299.

Leucht S, Cipriani A, Spineli L et al. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382: 951–962.

Lieberman JA, Stroup TS, Mcevoy JP et al. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353: 1209–1223.

Lima AR, Bacalcthuk J, Barnes TR et al. (2004). Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev, CD001946.

Lin CC, Huang TL (2013). Lorazepam-diazepam protocol for catatonia in schizophrenia: a 21-case analysis. Compr Psychiatry 54: 1210–1214.

Lin CC, Hung YY, Tsai MC et al. (2017). The lorazepam and diazepam protocol for catatonia due to general medical condition and substance in liaison psychiatry. PLoS One 12: e0170452.

Littrell K, Magill AM (1993). The effect of clozapine on preexisting tardive dyskinesia. J Psychosoc Nurs Ment Health Serv 31: 14–18.

Lohr JB, Eidt CA, Abdulrazzaq Alfaraj A et al. (2015). The clinical challenges of akathisia. CNS Spectr 20 (Suppl. 1): 1–14. quiz 15-6.

Louza MR, Bassitt DP (2005). Maintenance treatment of severe tardive dyskinesia with clozapine: 5 years' follow-up. J Clin Psychopharmacol 25: 180–182.

Low DA, Xu J, Tibrewal P et al. (2017). Parenteral lorazepam's unavailability in Australia and the impact for catatonic patients. Aust N Z J Psychiatry 51: 198.

Luchini F, Medda P, Mariani MG et al. (2015). Electroconvulsive therapy in catatonic patients: efficacy and predictors of response. World J Psychiatry 5: 182–192.

Margolese HC, Chouinard G, Kolivakis TT et al. (2005). Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 1: pathophysiology and mechanisms of induction. Can J Psychiatry 50: 541–547.

Mastain B, Vaiva G, Guerouaou D et al. (1995). Favourable effect of zolpidem on catatonia. Rev Neurol 151: 52–56.

Mentzel CL, Tenback DE, Tijssen MA et al. (2012). Efficacy and safety of deep brain stimulation in patients with medication-induced tardive dyskinesia and/or dystonia: a systematic review. J Clin Psychiatry 73: 1434–1438.

Mentzel CL, Bakker PR, van Os J et al. (2017). Effect of antipsychotic type and dose changes on tardive dyskinesia and parkinsonism severity in patients with a serious mental illness: the Curaçao extrapyramidal syndromes study XII. J Clin Psychiatry 78(3): e279–e285.

Mentzel TQ, van der Snoek R, Lieverse R et al. (2018). Clozapine monotherapy as a treatment for antipsychotic-induced tardive dyskinesia: a meta-analysis. J Clin Psychiatry 79: 17r11852.

Miller CH, Fleischhacker WW (2000). Managing antipsychotic-induced acute and chronic akathisia. Drug Saf 22: 73–81.

Miller DD, Caroff SN, Davis SM et al. (2008). Extrapyramidal side-effects of antipsychotics in a randomised trial. Br J Psychiatry 193: 279–288.

Mittal VA, Jalbrzikowski M, Daley M et al. (2011). Abnormal movements are associated with poor psychosocial functioning in adolescents at high risk for psychosis. Schizophr Res 130: 164–169.

Modestin J, Wehrli MV, Stephan PL et al. (2008). Evolution of neuroleptic-induced extrapyramidal syndromes under long-term neuroleptic treatment. Schizophr Res 100: 97–107.

Moore NC, Lewitt PA, Gershon S (1992). Reduction of dyskinesias and psychiatric disability with clozapine over different time courses. J Psychopharmacol 6: 514–518.

Muneoka K, Kanahara N, Kimura S (2017). Switching to aripiprazole for the treatment of residual mutism resulted in distinct clinical courses in two catatonic schizophrenia cases. SAGE Open Med Case Rep 5: 1–3.

Muzyk AJ, Cvelich RG, Rivelli SK (2012). Metoclopramide-induced tardive respiratory dyskinesia. J Neuropsychiatry Clin Neurosci 24: E37–E38.

O'Brien A (2016). Comparing the risk of tardive dyskinesia in older adults with first-generation and second-generation antipsychotics: a systematic review and meta-analysis. Int J Geriatr Psychiatry 31: 683–693.

Oh GH, Yu JC, Choi KS et al. (2015). Simultaneous comparison of efficacy and tolerability of second-generation antipsychotics in schizophrenia: mixed-treatment comparison analysis based on head-to-head trial data. Psychiatry Investig 12: 46–54.

Oldham MA (2018). The probability that catatonia in the hospital has a medical cause and the relative proportions of its causes: a systematic review. Psychosomatics 59: 333–340.

Oruch R, Pryme IF, Engelsen BA et al. (2017). Neuroleptic malignant syndrome: an easily overlooked neurologic emergency. Neuropsychiatr Dis Treat 13: 161–175.

Paparrigopoulos T, Tzavellas E, Ferentinos P et al. (2009). Catatonia as a risk factor for the development of neuroleptic malignant syndrome: report of a case following treatment with clozapine. World J Biol Psychiatry 10: 70–73.

Payee H, Chandrasekaran R, Raju GV (1999). Catatonic syndrome: treatment response to lorazepam. Indian J Psychiatry 41: 49–53.

Peglow S, Prem V, McDaniel W (2013). Treatment of catatonia with zolpidem. J Neuropsychiatry Clin Neurosci 25: E13.

Pelzer A, van der Heijden FM, den Boer E (2018). Systemic review of catatonia treatment. Neuropsychiatr Dis Treat 14: 317–326.

Perry LA, Ramson D, Stricklin S (2018). Mirtazapine adjunct for people with schizophrenia. Cochrane Database Syst Rev 2018(5): CD011943. https://doi.org/10.1002/14651858.CD011943.pub2.

Petrides G, Divadeenam KM, Bush G et al. (1997). Synergism of lorazepam and electroconvulsive therapy in the treatment of catatonia. Biol Psychiatry 42: 375–381.

Pinninti NR, Faden J, Adityanjee A (2015). Are second-generation antipsychotics useful in tardive dystonia? Clin Neuropharmacol 38: 183–197.

Pommepuy N, Januel D (2002). Catatonia: resurgence of a concept. A review of the international literature. Encéphale 28: 481–492.

Praharaj SK, Kongasseri S, Behere RV et al. (2015). Mirtazapine for antipsychotic-induced acute akathisia: a systematic review and meta-analysis of randomized placebo-controlled trials. Ther Adv Psychopharmacol 5: 307–313.

Pringsheim T, Gardner D, Addington D et al. (2018). The assessment and treatment of antipsychotic-induced akathisia. Can J Psychiatry 63 (11): 719–729.

Puthane VH, Thirthalli J, Muralidhanran K (2012). Double-blind randomized controlled study showing symptomatic and cognitive superiority of bifrontal over bitemporal electrode placement during electroconvulsive therapy for schizophrenia. Brain Stimul 6: 210–217.

Rao AS, Camilleri M (2010). Review article: metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther 31: 11–19.

Rascle C, Thomas P, Maron M et al. (1997). Catatonia relief with zolpidem: an open study. Eur Neuropsychopharmacol 7: S277.

Rasmussen SA, Mazurek MF, Rosebush PI (2016). Catatonia: our current understanding of its diagnosis, treatment and pathophysiology. World J Psychiatry 6: 391–398.

Rathbone J, Soares-Weiser K (2006). Anticholinergics for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev, (4): CD003727.

Raveendranathan D, Narayanaswamy JC, Reddi SV (2012). Response rate of catatonia to electroconvulsive therapy and its clinical correlates. Eur Arch Psychiatry Clin Neurosci 262: 425–430.

Reulbach U, Dutsch C, Biermann T et al. (2007). Managing an effective treatment for neuroleptic malignant syndrome. Crit Care 11: R4.

Ribeiro ELA, De Mendonca Lima T, Vieira MEB et al. (2018). Efficacy and safety of aripiprazole for the treatment of schizophrenia: an overview of systematic reviews. Eur J Clin Pharmacol74: 1215–1233. https://doi.org/10.1007/s00228-018-2498-1.

Rosebush PI, Mazurek MF (2010). Catatonia and its treatment. Schizophr Bull 36: 239–242.

Ryu S, Yoo JH, Kim JH et al. (2015). Tardive dyskinesia and tardive dystonia with second-generation antipsychotics in non-elderly schizophrenic patients unexposed to first-generation antipsychotics: a cross-sectional and retrospective study. J Clin Psychopharmacol 35: 13–21.

Sachdev P (1995). The epidemiology of drug-induced akathisia: part I. Acute akathisia. Schizophr Bull 21: 431–449.

Sako W, Morigaki R, Mizobuchi Y et al. (2011). Bilateral pallidal deep brain stimulation in primary Meige syndrome. Parkinsonism Relat Disord 17: 123–125.

Scorr L, Factor S (2018). VMAT2 inhibitors for the treatment of tardive dyskinesia. J Neurol Sci 15 (389): 43–47.

Shi J, Tan YL, Wang ZR et al. (2016). Ginkgo biloba and vitamin E ameliorate haloperidol-induced vacuous chewing movement and brain-derived neurotrophic factor expression in a rat tardive dyskinesia model. Pharmacol Biochem Behav 148: 53–58.

Sienaert P, Rooseleer J, De Fruyt J (2011). Measuring catatonia: a systematic review of rating scales. J Affect Disord 135: 1–9.

Sienaert P, Dhossche DM, Gazdag G (2013). Adult catatonia: etiopathogenesis, diagnosis and treatment. Neuropsychiatry 3: 391–399.

Sienaert P, Dhossche DM, Vancampfort D et al. (2014). A clinical review of the treatment of catatonia. Front Psych 5: 181.

Skidmore F, Weiner WJ, Burke R (2005). Neuroleptic-induced tardive dyskinesia variants. In: SA Factor, AE Lang, WJ Weiner (Eds.), Drug induced movement disorders, Blackwell Publishing, Massachusetts.

Slotema CW, van Harten PN, Bruggeman R et al. (2008). Botulinum toxin in the treatment of orofacial tardive dyskinesia: a single blind study. Prog Neuropsychopharmacol Biol Psychiatry 32: 507–509.

Soares-Weiser K, Fernandez HH (2007). Tardive dyskinesia. Semin Neurol 27: 159–169.

Speelman JD, Contarino MF, Schuurman PR et al. (2010). Deep brain stimulation for dystonia: patient selection and outcomes. Eur J Neurol 17 (Suppl. 1): 102–106.

Spivak B, Mester R, Abesgaus J et al. (1997). Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism, and chronic akathisia in schizophrenic patients. J Clin Psychiatry 58: 318–322.

Strawn JR, Keck Jr PE, Caroff SN (2007). Neuroleptic malignant syndrome. Am J Psychiatry 164: 870–876.

Strous RD, Alvir JM, Robinson D et al. (2004). Premorbid functioning in schizophrenia: relation to baseline symptoms, treatment response, and medication side effects. Schizophr Bull 30: 265–278.

Svetel M, Ivanovic N, Marinkovic J et al. (2004). Characteristics of dystonic movements in primary and symptomatic dystonias. J Neurol Neurosurg Psychiatry 75: 329–330.

Tabbane K, Halayem S, Joober R (2016). Clozapine for the management of persistent catatonia. J Psychiatry Neurosci 41: E81–E82.

Tarsy D, Kaufman D, Sethi KD et al. (1997). An open-label study of botulinum toxin A for treatment of tardive dystonia. Clin Neuropharmacol 20: 90–93.

Tenback DE, van Harten PN (2011). Epidemiology and risk factors for (tardive) dyskinesia. Int Rev Neurobiol 98: 211–230.

Tenback DE, van Harten PN, van Os J (2009). Non-therapeutic risk factors for onset of tardive dyskinesia in schizophrenia: a meta-analysis. Mov Disord 24: 2309–2315.

Tenback DE, van Harten PN, Slooff CJ et al. (2010). Incidence and persistence of tardive dyskinesia and extrapyramidal symptoms in schizophrenia. J Psychopharmacol 24: 1031–1035.

Thirthalli J, Phutane VH, Muralidharan K et al. (2009). Does catatonic schizophrenia improve faster with electroconvulsive therapy than other subtypes of schizophrenia? World J Biol Psychiatry 10: 772–777.

Thomas P, Rascle C, Mastain B et al. (1997). Test for catatonia with zolpidem. Lancet 349: 702.

Thomas JE, Caballero J, Harrington CA (2015). The incidence of akathisia in the treatment of schizophrenia with Aripiprazole, Asenapine and Lurasidone: a meta-analysis. Curr Neuropharmacol 13: 681–691.

Touma KTB, Scarff JR (2018). Valbenazine and Deutetrabenazine for tardive dyskinesia. Innov Clin Neurosci 15: 13–16.

Trollor JN, Sachdev PS (1999). Electroconvulsive treatment of neuroleptic malignant syndrome: a review and report of cases. Aust N Z J Psychiatry 33: 650–659.

Trollor JN, Chen X, Chitty K et al. (2012). Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. Br J Psychiatry 201: 52–56.

Unal A, Bulbul F, Alpak G et al. (2013). Effective treatment of catatonia by combination of benzodiazepine and electroconvulsive therapy. J ECT 29: 206–209.

van den Eede F, van Hecke J, van Dalfsen A et al. (2005). The use of atypical antipsychotics in the treatment of catatonia. Eur Psychiatry 20: 422–429.

van der Heijden FM, Tuinier S, Arts NJ et al. (2005). Catatonia: disappeared or under-diagnosed? Psychopathology 38: 3–8.

van der Markt A, Heller HM, van Exel E (2015). A woman with catatonia, what to do after ECT fails: a case report. J ECT 32 (3): e6–e7.

van Harten PN (2002). Drug-induced akathisia. Ned Tijdschr Geneeskd 146: 110–114.

van Harten PN, Hovestadt A (2006). Botulinum toxin as a treatment for tardive dyskinesia. Mov Disord 21: 1276–1277.

van Harten PN, Kahn RS (1999). Tardive dystonia. Schizophr Bull 25: 741–748.

van Harten PN, Kamphuis DJ, Matroos GE (1996a). Use of clozapine in tardive dystonia. Prog Neuropsychopharmacol Biol Psychiatry 20: 263–274.

van Harten PN, Matroos GE, Hoek HW et al. (1996b). The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia the curacao extrapyramidal syndromes study: I. Schizophr Res 19: 195–203.

van Harten PN, Hoek HW, Matroos GE et al. (1997). The interrelationships of tardive dyskinesia, parkinsonism, akathisia and tardive dystonia: the curacao extrapyramidal syndromes study II. Schizophr Res 26: 235–242.

van Harten PN, Hoek HW, Matroos GE et al. (1998). Intermittent neuroleptic treatment and risk for tardive dyskinesia: curacao extrapyramidal syndromes study III. Am J Psychiatry 155: 565–567.

van Harten PN, Hoek AW, Matroos GE et al. (2004). The incidence of tardive dystonia and tardive dyskinesia in patients on long-term antipsychotic treatment. Schizophr Res 67: 185.

van Harten PN, Hoek HW, Matroos GE et al. (2006). Incidence of tardive dyskinesia and tardive dystonia in African Caribbean patients on long-term antipsychotic treatment: the curacao extrapyramidal syndromes study V. J Clin Psychiatry 67: 1920–1927.

van Harten PN, Matroos GE, van Os J (2008). The course of tardive dystonia in Afro Caribbean patients, a population-based study: the curacao extrapyramidal syndromes study: VII. Schizophr Res 98: 79–83.

van Harten PN, Bakker PR, Mentzel CL et al. (2014). Movement disorders and psychosis, a complex marriage. Front Psych 5: 190.

Verdura Vizcaínoa EJ, Sanza DB, Sanz-Fuentenebro J (2011). Electroconvulsive therapy as treatment for malignant neuroleptic syndrome. Rev Psiquiatr Salud Ment 4: 169–176.

Zoons E, Dijkgraaf MG, Dijk JM et al. (2012). Botulinum toxin as treatment for focal dystonia: a systematic review of the pharmaco-therapeutic and pharmaco-economic value. J Neurol 259: 2519–2526.