Chapter 19
Pharmacological Therapies for Machado-Joseph Disease

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Abstract Machado-Joseph disease (MJD), also known as Spinocerebellar Ataxia type 3 (SCA3), is the most common autosomal dominant ataxia worldwide. MJD integrates a large group of disorders known as polyglutamine diseases (polyQ). To date, no effective treatment exists for MJD and other polyQ diseases. Nevertheless, researchers are making efforts to find treatment possibilities that modify the disease course or alleviate disease symptoms. Since neuroimaging studies in mutation carrying individuals suggest that in nervous system dysfunction begins many years before the onset of any detectable symptoms, the development of therapeutic interventions becomes of great importance, not only to slow progression of manifest disease but also to delay, or ideally prevent, its onset. Potential therapeutic targets for MJD and polyQ diseases can be divided into (i) those that are aimed at the polyQ proteins themselves, namely gene silencing, attempts to enhance mutant protein degradation or inhibition/prevention of aggregation; and (ii) those that intercept the toxic downstream effects of the polyQ proteins, such as mitochondrial dysfunction and oxidative stress, transcriptional abnormalities, UPS impairment, excitotoxicity, or activation of cell death. The existence of relevant animal models and the recent contributions towards the identification of putative molecular mechanisms underlying MJD are impacting on the development of new drugs. To date only a few preclinical trials were conducted, nevertheless some had very promising results and some candidate drugs are close to being tested in humans. Clinical trials for MJD are also very few to date and their results not very promising, mostly due to trial design constraints. Here, we provide an overview of the pharmacological therapeutic strategies for MJD studied in animal models and patients, and of their possible translation into the clinical practice.

Keywords PolyQ diseases · Machado-Joseph disease · Pharmacologic therapy

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19.1 Machado-Joseph Disease or Spinocerebellar Ataxia Type 3

Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), is known to exist worldwide [1], representing the most common dominantly inherited ataxia (Reviewed in [1–3]) and the second most common polyQ disease [4]. In the last years a large effort has been put forward towards the understanding of the pathologic mechanism(s) underlying polyQ diseases, however, and unfortunately, the therapeutic approaches and drug development did not reach the desirable outcomes yet. Despite the increasing number of therapeutic strategies assessed in mouse models of polyQ diseases (around 250 preclinical therapeutic trials have already been described) [5], there are no effective treatments for these disorders, including MJD, and currently available therapeutic approaches are only able to provide limited symptomatic relief (Reviewed in [6, 7]).

The core clinical feature in MJD is a slowly progressive ataxia starting in adulthood, being the average age at onset of 40 years and the mean survival time of 21 years [8]. Numerous other clinical symptoms, including weight loss, dystonia, dysarthria, spasticity, rigidity, fasciculations, postural instability, proprioceptive loss, dysphagia, amyotrophy, corticospinal and autonomic nervous system dysfunctions and neuropathy, are also frequently observed in MJD patients [9–11]. Non-motor symptoms are also present, such as cramps, fatigue, sleep disturbances, mild cognitive affection and mood-related diseases [12–16]. Neuropathologically, MJD is characterized by neuronal loss in the cerebellum, *substantia nigra*, striatum, thalamus, pontine nuclei, spinal cord and cranial nerves, precerebellar brainstem nuclei, cholinergic and dopaminergic midbrain, as well as visual, auditory, vestibular, somatosensory, and ingestion and urination-related systems (Reviewed in [11]). Retained integrity of the cortical and subcortical regions of the limbic system and mild degeneration of cerebral and cerebellar cortices, white matter of cerebellum, inferior olive and Purkinje cells, are also characteristic of MJD [11]. The ataxin-3 protein (the MJD disease protein) is expressed ubiquitously and when it bears the expanded allele it tends to aggregate forming neuronal nuclear inclusion bodies (NNIs) in the brain [17, 18]. These NNIs are present in functionally affected and non-affected brain regions, indicating that there is no direct correlation between the occurrence of these protein aggregates and neuronal dysfunction [11, 19, 20]. Axonal aggregates have also been found in human patients and, as the intranuclear aggregates, they were immunopositive for ubiquitin and p62; one can hypothesize that axonal inclusions might be detrimental to axonal transport mechanisms, contributing to degeneration of nerve cells in MJD [21].

The clinical presentation of MJD is highly pleomorphic and led to the definition of four clinical sub-phenotypes: **type I**, characterised by the predominance of pyramidal and extrapyramidal anomalies, in addition to ataxia and other signs, with an early age-at-onset and fast progression; **type II**, with typical cerebellar ataxia, progressive external ophthalmoplegia and pyramidal signs appearing at an intermediate age; **type III**, with late onset and slow progression of peripheral signs,

such as loss of proprioception and muscle atrophies; and **type IV**, the rarest, characterised by the presence of Parkinsonic signs, associated to the core clinical features [10, 22, 23].

Here, we provide an overview of the current situation concerning small molecule therapeutics for MJD, including a brief description of the symptomatic therapies used in the clinics to improve patients' daily life, followed by a section on the recent drug discovery and development efforts, outlining the disease-modifying therapies tested so far in animal models of this disorder. In the end, we also provide a summary of the clinical trials performed to date in MJD patients.

19.2 Symptomatic Therapies for Machado-Joseph Disease

Despite the lack of efficacious disease-modifying therapies for MJD to date, several treatments, including specific drugs and multi-professional supportive approaches, are used to ameliorate neurological symptoms and increase the quality of life of the patients (Reviewed in [24], *updated in 2015*).

Non-pharmacological therapies include genetic counselling [25, 26], speech therapy, exercise/physiotherapy [27, 28], and occupational therapy [29]. The occupational therapy combined with antidepressants is thought to be helpful to fight the depression symptoms reported in MJD [30].

The pharmacological therapies prescribed by the physicians are mainly based on the knowledge of other related diseases or based on the patient's needs. Yet, the efficacy of those therapies has not been proven scientifically in MJD patients. Importantly, none of the clinical trials performed to date in MJD patients were based on data obtained in animal models of the disease. Nowadays, and with available animal models that closely mimic the human condition, the connection between preclinical and clinical studies should be strengthened. Pharmacological therapy includes levodopa or dopamine agonists for the restless leg syndrome as well as for the parkinsonism-like symptoms [31]. Adverse events may occur with levodopa treatment, namely worsening of the motor symptoms as shown for Parkinson's disease patients [32]. Modafinil, a psychostimulant, can be used to improve daytime fatigue, which is very frequent in MJD, and mexiletine or carbamazepine for cramps [33]. Together, these examples show that symptomatic MJD patients may benefit from available pharmacological approaches, which provide an important combination for the quality of life and the patients' feeling of independence.

19.3 Disease-Modifying Therapies for Machado-Joseph Disease: Lessons from Preclinical Trials

Despite the existence of a variety of MJD rodent models ([34] reviewed in [35]) and their potentialities, only a few preclinical trials have been performed until now using these models (see Table 19.1), and even less have then been translated to

Table 19.1 Preclinical trials performed in MJD mouse models using pharmacological approaches

Therapeutic molecule	Dosage	REF	Target/action	Treatment onset	Treatment duration (weeks)	Route of administration	Control groups	Outcome		Model
								Phenotype	Pathology	
Dantrolene	5 mg/kg	Chen et al. [85]	Stabilizer of intracellular Ca^{2+} signaling	Post-symptomatic	40	Food supplementation	Wild-type animals (treated and vehicle); MJD mice vehicle	Improvement in the beam walk test; improved gait deficits;	Restored brain weight; restored neuronal loss in PN; SN-TH neuronal cell loss is improved	Cemal et al. [83]
CCI-779	20 mg/kg	Menzies et al. [48]	Autophagy inducer	Post-symptomatic	8	i.p injection (3x/week)	Wild-type animals (treated and vehicle)-data not shown; MJD mice vehicle	Improvement in Rotarod (no phenotype was detected in basal conditions)	Reduced aggregate number in the motor cortex; reduction in soluble ataxin-3	Bichelmeier et al. [57]
Sodium butyrate	400 and 800 mg/kg	Chou et al. [78]	HDAC inhibitor	Pre-symptomatic	36	i.p injection (daily)	MJD mice vehicle	Prevention of weight loss; improvement in the rotarod; improved ataxic symptoms; improved hypoactivity; prolonged survival	Ameliorates mutant ataxin-3-induced degeneration of Purkinje neurons; restored hypoacetylation status in cerebellum	Chou et al. [62]
H1152	10 mg/kg	Wang et al. [63]	Rho-kinase (ROCK) inhibitor	Pre-symptomatic	12	i.p injection (daily)	Wild-type animals (treated); MJD mice vehicle	Partial improvement in the rotarod; increase in locomotor activity deficit	Reduction of ataxin-3 levels in the cerebellum, cerebral cortex, pontine nuclei or spinal cord; prevention of neuronal loss in the pontine nuclei	Chou et al. [62]

(continued)

Table 19.1 (continued)

Therapeutic molecule	Dosage	REF	Target/action	Treatment onset	Treatment duration (weeks)	Route of administration	Control groups	Outcome		Model
								Phenotype	Pathology	
Caffeine	1 g/L	Goncalves et al. [89]	Non-selective adenosine receptor antagonist	Pre-symptomatically	12	Drinking water	C57Bl6 animals vehicle (expressing mutant and wild-type ataxin-3 in the striatum)	ND	Ameliorates mutant ataxin-3 induced neurodegeneration; reduction in inclusions in the basal ganglia; reactive gliosis was reduced	Goncalves et al. [89]
17-DMAG	25 mg/kg	Silva-Fernandes et al. [42]	Hsp90 inhibitor	Pre-symptomatic	25	i.p injection (3x/week)	Wild-type animals (treated and vehicle); MJD mice vehicle	Delayed and improved motor deficits onset. Improved swimming performance, rotarod deficits and balance problems	Reduced aggregate number in the pontine nuclei and soluble ataxin-3 protein levels; decreased the number of pyknotic cells in the pontine nuclei	Silva-Fernandes et al. [42]
Lithium chloride	10.4 mg/kg	Duarte-Silva et al. [59]	Autophagy inducer	Pre-symptomatic	19	i.p injection (3x/week)	Wild-type animals (treated and vehicle); MJD mice vehicle	No overall effect; reduction of the tremors at endstage	No effect on mutant ataxin-3 levels	Silva-Fernandes et al. [42]
Citalopram	8 and 13 mg/kg	Teixeira-Castro et al. [101]	Selective serotonin reuptake inhibitor	Pre-symptomatic	29	Drinking water	Wild-type animals (treated and vehicle); MJD mice vehicle	Improved body weight, gait and motor deficits (footprinting, beam walk and motor swimming tests)	Reduced ataxin-3-posivite aggregates in several affected brain regions; reduced astrogliosis; increased number of ChAT + cells in the spinal cord and in the 7 N; increased Calbindin staining in Purkinje cells	Silva-Fernandes et al. [42]

(continued)

Table 19.1 (continued)

Therapeutic molecule	Dosage	REF	Target/action	Treatment onset	Treatment duration (weeks)	Route of administration	Control groups	Outcome		Model
								Phenotype	Pathology	
Valproic acid	200 mg/kg	Esteves et al. [79]	HDCA inhibitor	Pre-symptomatic	25	i.p (5 consecutive days/week)	Wild-type animals (treated and vehicle); MJD mice vehicle	Minor effects on body weight, balance problems, exploratory activity, swimming deficits and motor uncoordination in the rotarod	No effect on mutant ataxin-3-positive neuronal aggregates	Silva-Fernandes et al. [42]
Lithium chloride + CCI-779	10.4 mg/kg + 20 mg/kg	Duarte-Silva et al. [61]	Autophagy inducers	Pre-symptomatic	19	i.p injection (3x/week)	Wild-type animals (treated and vehicle); MJD mice vehicle	No overall effect in several behavior paradigms; combined therapy showed to be toxic to transgenic and wild-type mice	Reduction of soluble mutant ataxin-3 and the number of neuronal aggregates in the pontine nuclei	Silva-Fernandes et al. [42]
Riluzole	10 mg/kg	Schmidt et al. [110]	Glutamate antagonist	Post-symptomatic	40	Drinking water	Single transgenic for the MJD responder (treated and vehicle)	No improvement on motor deficits measured by rotarod, on home cage activity or body weight	Reduction of the soluble ataxin-3 level and an increase in ataxin-3 positive accumulations; reduction of calbindin expression in Purkinje cells in riluzole treated mice	Boy et al. [109]
Resveratrol	10 mg/kg	Cunha-Santos et al. [94]	Sirtuin 1 inducer	Post-symptomatic	8	i.p injection (daily)	MJD mice vehicle	Improved motor deficits and balance	Restored SIRT1 mRNA levels. Neuropathology was not evaluated	Torashima et al. [99]

clinical trials. Those studies were performed considering different approaches: (i) more directly targeting mutant ataxin-3 synthesis, folding and degradation and (ii) reducing the downstream deleterious effects of mutant ataxin-3 accumulation. The hypothesized pathogenic mechanism(s) involved in MJD and discussed throughout this chapter are represented in Fig. 19.1, as well as the possible therapeutic targets.

19.3.1 Mutant Ataxin-3 Refolding and Degradation: Autophagy and Proteasome Inducers

Restoration of global protein homeostasis, or proteostasis, is a promising approach to reduce the toxicity of mutant ATXN3 in MJD. Several studies in rodent models demonstrated the efficacy of activating the cellular machinery involved in maintaining adequate conformation and solubility of proteins or, in case this fails, send them for degradation, such as molecular chaperones, the ubiquitin-proteasome system (UPS) and autophagy, which will be discussed hereafter.

For instance, Hsp90 inhibitors are known to possess the unique pharmacological effect of inducing a heat stress response and, in addition to their use as anticancer agents, have also been developed as pharmacological HSP inducers for application in protein folding disorders [36, 37]. Several studies demonstrated the positive effects of 17-AAG and its analogues (including 17-DMAG, which is less toxic) as Hsp90 inhibitors in models of polyQ diseases [38–41]. The efficacy of 17-DMAG in improving the behavioral deficits was tested in the CMVMJD135 mice [42]. In this study it was shown that the behavioral deficits were transiently improved by 17-DMAG administration and neuropathologic features were ameliorated. Surprisingly, 17-DMAG did not induce the HSR in the brain of CMVMJD135 animals as expected. However, the protein levels of mutant ataxin-3 as well as the aggregate load were diminished after 17-DMAG treatment suggesting that other mechanism(s) would be occurring in the cells. Indeed, it was proposed that 17-DMAG was inducing autophagy and therefore probably the degradation of mutant ataxin-3 through this mechanism (not excluding others, as the UPS). In spite of the promising results in mouse models, establishing proof of concept, 17-DMAG is known to exert several important adverse effects in humans [43], which must be taken in consideration given the expected need for chronic treatment of MJD patients. Chemical modifications should be conducted in 17-DMAG to decrease its toxicity while keeping its beneficial effects; only after that should such an approach be considered for clinical trials in MJD.

Autophagy induction seems to be a promising target to modulate protein aggregation in polyQ diseases and, in addition to the abovementioned results, there is an extensive body of literature demonstrating its beneficial effects in polyQ diseases [43–56]. In order to verify the therapeutic efficacy of autophagy induction in MJD, Menzies and colleagues used the mouse model generated by Bichelmeier et al. [57]

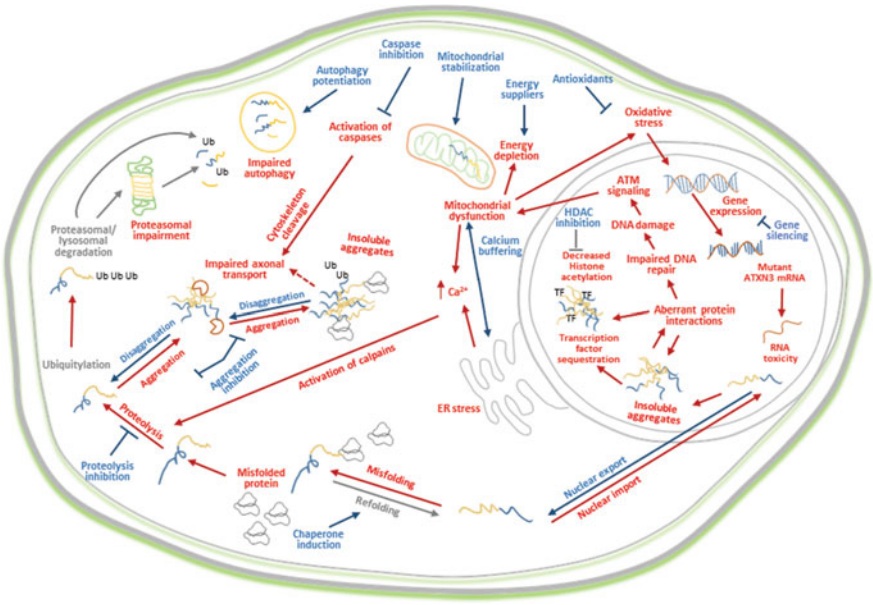

Fig. 19.1 Schematic representation of the potential pathogenic mechanisms underlying MJD and possible therapeutic targets. Intracellular candidate pathogenesis pathways in MJD are represented in red. These include the formation of cytoplasmic and nuclear aggregates/inclusions, transcriptional deregulation, mitochondrial dysfunction, impairment of degradation mechanisms (autophagy/proteasome) and activation of caspases/calpains. Possible intracellular therapeutic targets are represented in blue

which they chronically treated with an autophagy inducer—temsirolimus (codenamed CCI-779), a rapamycin analog. Although the authors were not able to reproduce the phenotype previously described for this model [57], at the end of a two months preclinical trial they report that treated-MJD animals performed better in the accelerating rod when compared to placebo-treated mice, and that this compound had no effect in wild-type (WT) animals in the rotarod. Also, temsirolimus was able to reduce mutant ataxin-3 aggregates in the motor cortex and the soluble cytoplasmic, but not nuclear, mutant ataxin-3 in total brain extracts. Finally, the authors performed a microarray study at basal conditions and after temsirolimus treatment. Overall, the transcriptional alterations found were very small, probably correlating to the absence of a clear phenotype in this cohort of MJD mice. Yet, it was possible to identify genes with decreased expression in MJD-vehicle mice, which was increased after temsirolimus treatment; the opposite effect was not found [48]. The potential beneficial effects of autophagy induction were further reinforced in studies using beclin-1 overexpression in rodent models of MJD [58]. Thus, and also considering the beneficial effects of 17-DMAG, other autophagy inducers were tested in the CMVMJD135 mice: lithium chloride and CCI-779. Unexpectedly, the use of lithium chloride had no overall effect on the behavioral deficits of CMVMJD135 mice, in spite of activating autophagy as expected [59]. Accordingly,

a human clinical trial using lithium carbonate was performed in the same year, demonstrating that albeit well tolerated, lithium had no major impact on disease progression in MJD patients [60] (see Sect. 19.4 in the present chapter). In another attempt to increase autophagy, a combination of two autophagy inducers acting independently and dependently of mTOR—lithium and CCI-779, respectively—was tested in the CMVMJD135 mouse model. This combinatory therapy showed no beneficial effects and even proved to be deleterious to both transgenic and wild-type mice, affecting neurological function and general health [61], at doses shown to be safe in mice when administered alone [48, 59]. These results suggest that overactivation of autophagy could also be dangerous, however, other effects of the drug combination cannot be excluded.

Using the mouse model developed by their team [62], Wang and colleagues developed a preclinical trial using H1152, a Rho-kinase (ROCK) inhibitor [63]. ROCK is a kinase and acts as the downstream effector of small GTP-binding proteins of the Rho subfamily, and its abnormal activation has been implicated in several neurodegenerative diseases [64]. Also, ROCK inhibitors were shown to decrease the levels of mutant huntingtin in brain as well as improve motor function in a mouse model of Huntington's disease (HD) [65]. This study confirmed that H1152 could also decrease the brain level of pathogenic ataxin-3 and exert a therapeutic effect on the MJD mouse model. The authors tested several ROCK inhibitors in vitro and showed that H1152 was the most potent in reducing ataxin-3 protein levels, and that acted by increasing proteasome activity. Daily intraperitoneal injections of H1152 in the MJD mice improved motor coordination and locomotor activity deficits. H1152 administration significantly decreased mutant ataxin-3 levels in the cerebellum, cerebral cortex, pontine nuclei and spinal cord and decreased the cell death (reduction in NeuN positive cells) observed in the pontine nuclei of vehicle-treated transgenic animals [63]. Fasudil, a first-generation ROCK inhibitor, has been studied widely in clinical trials for the treatment of pulmonary arterial hypertension as well as for subarachnoid hemorrhage [66], constituting a safe drug in humans. A phase II clinical trial is ongoing for the study of its safety and efficacy in amyotrophic lateral sclerosis patients (NCT01935518). Indeed, its protective effects were recently shown in a model of HD [67]. In this sense, the inhibition of ROCK can be regarded as a promising avenue for therapeutic intervention in various neurological disorders, including MJD and other polyQ diseases.

19.3.2 Therapies Targeting Downstream Molecular Events

19.3.2.1 Transcriptional Regulation

Transcriptional deregulation is a unifying feature of polyQ disorders [68–73]; however, the relationship between polyQ-induced deregulation of gene expression and the ongoing degenerative processes remains unclear.

More than 20 nuclear proteins relevant for transcription are known to interact with polyQ disease associated-proteins [69, 74]. Mutant ataxin-3 has been shown to interact abnormally with several proteins involved in the transcription machinery, namely CREB-binding protein (CBP) and p300/CREBBP associated factor (PCAF), suppressing their histone acetyltransferase activity [72, 75]. Overexpression of some of these transcription regulators was shown to overcome polyQ toxicity, both in cellular models for MJD, Spinal and Bulbar Muscular Atrophy (SBMA), and HD [70, 76] as well as in vivo, in a polyQ model in Drosophila [71]. This suggests that expanded polyQ proteins may contribute for the depletion of key transcriptional regulators with toxic effects to the cell and reinforces the idea of an important role for transcription deregulation in polyQ pathogenesis. Acetylation of histones relaxes the DNA structure, promoting transcription, whereas hypoacetylation represses gene activity [77]. The equilibrium of histone acetylation/deacetylation is controlled by histone acetyltransferases (HATs) and deacetylases (HDACs).

Previously, based on expression data, Chou and collaborators suggested that a global transcriptional deregulation was occurring in the cerebellum of a MJD transgenic model [62]. More specifically, they have shown a generalized hypoacetylation of H3 and H4. In order to modulate these alterations in the transcriptome, the same authors treated their mouse model with sodium butyrate (SB), an HDAC inhibitor. They observed that daily administration of SB was able to revert histone hypoacetylation as well as the transcription downregulation in the cerebellum. Importantly, SB treatment improved motor performance of transgenic animals in the rotarod, an effect that was less evident in later stages. The gait-related symptoms, quantified through the footprint pattern, were also ameliorated with SB, as well as the spontaneous locomotor activity, body weight loss and survival [78].

In contrast, Esteves S and colleagues, demonstrated that chronic treatment of the CMVMJD135 mice with valproic acid (VPA), also known to act as an HDAC inhibitor led to limited effects concerning the improvement of motor deficits and had no effect on mutant ataxin-3 aggregation in the brain. Nevertheless, VPA treatment increased the levels of GRP78, an endoplasmic reticulum chaperone involved in the folding of newly synthetized proteins and in the translocation of aberrant proteins for degradation by the proteasome, which might explain the small improvement in motor coordination seen after a long treatment duration [79]. These results contrast with the findings of a study in human patients, in which a beneficial effect was observed (see Sect. 19.4 in the present chapter).

19.3.2.2 Calcium Signaling Stabilizers

Calcium signaling is thought to play an important role in polyQ pathogenesis. This hypothesis is based on previous studies demonstrating that mutant huntingtin can bind and activate specifically type 1 inositol 1,4,5-triphosphate receptors (InsP3R1, an intracellular calcium release channel), influencing calcium signaling [80]. Deranged calcium signaling was also observed in neuronal primary cultures from the YAC128 HD mouse model [81, 82]. Later on, mutant ATXN3 was also proven

to bind to InsP3R1 and to perturb calcium signaling. Taking advantage of the YAC transgenic model of MJD generated by Cemal et al. in [83], Chen and collaborators performed a chronic treatment to these mice, using food supplemented with dantrolene. This compound is a ryanodine antagonist and a clinically relevant Ca^{2+} signaling stabilizer, being commonly used as a skeletal muscle relaxant to treat hyperthermia and muscle spasticity [84]. Dantrolene-treated MJD mice showed an improved performance in the balance beam test (taking less time to traverse the different beams, with a number of foot slips identical to WT), reduction of the crawling behavior seen in the MJD-vehicle group, and a significant improvement in the footprinting pattern. To evaluate the neuroprotective effect of dantrolene, the brains of the four groups used were weighed, however there was no improvement in this parameter. Dantrolene food supplementation did, nevertheless, diminish the loss of NeuN positive cells in the pontine nuclei and of TH-positive cells in the *substantia nigra* of MJD mice [85]. In spite of its beneficial effects, no further studies with this compound were performed in MJD patients. The known side effects of dantrolene originate in the central nervous system, and include drowsiness, lightheadedness, headaches, anorexia, diarrhea, nausea, and vomiting [86]. To our knowledge, no clinical trials with dantrolene have been performed in neurodegenerative diseases, suggesting that this compound might not be a good candidate for MJD treatment.

19.3.2.3 Neuroprotection

Neuronal dysfunction and synaptotoxicity are thought to play a major role in polyQ disease pathogenesis. Indeed, it was previously suggested that neuronal dysfunction may precede neurodegeneration and clinical symptoms in HD [87, 88]. In MJD, loss of synaptic markers was proposed to be an early feature in a lentiviral-based disease model, suggesting a putative role for ataxin-3 in the control of synapse function [89]. Furthermore, Silva-Fernandes and colleagues have shown the presence of a clear motor phenotype in the CMVMJD135 mouse model of MJD, without major early neuronal loss, suggesting once again, that neuronal dysfunction may precede neurodegeneration [42]. These hypotheses were not deeply explored, so far, in MJD; nevertheless, some compounds known to have neuroprotective effects have been tested in MJD models.

Treatment with caffeine (a non-selective adenosine receptor antagonist) as well as with selective blockers of the adenosine A_2A receptor ($A_{2A}R$) have been shown to be neuroprotective in several brain diseases, including HD [90–92]. In a study by Gonçalves et al., caffeine was administered to a lentiviral model of MJD (overexpression of human wild-type—atx3-27Q—or mutant ataxin-3-atx3-72Q) in the drinking water for 3 months (maximum), in a 1 g/L dose, corresponding to a human daily consumption of 5 cups of coffee. Chronic caffeine treatment rescued the striatal shrinkage observed in the mutant ATXN3 transduced animals and slightly reduced the number of pycnotic cells. Also, caffeine was able to avoid the loss of NeuN positive cells observed in the atx3-72Q animals. These data suggest

that chronic caffeine treatment is neuroprotective towards ataxin-3 overexpression in the striatum. Furthermore, loss of DARPP-32 staining volume, astrogliosis and putative microgliosis were improved in the treated group. Nevertheless, the beneficial effects of caffeine were shown to be transient. Finally, and intriguingly, caffeine-treated mice showed an increase in the number of nuclear inclusions when compared to water-drinking animals. These observations might indicate that the final stages of aggregation, visible neuronal inclusions, are protective rather than toxic [89], but this was not explored further. Several studies support the use of caffeine for different neurodegenerative diseases (reviewed in [93]). The neuroprotective effects of caffeine observed in the lentiviral-mediated model of MJD, and considering the well-define and side-effect profile, being in general well tolerated comparing to other drugs, support the use of antagonists of adenosine receptors as potential therapeutic tools to treat MJD and other polyQ diseases. Further studies in MJD patients should be performed to prove the clinical utility of this approach.

Recently, Cunha-Santos and colleagues tested the potential of resveratrol, a Sirtuin-1 (SIRT1) activator, as potential therapeutic strategy for MJD [94]. SIRT1 belongs to the group of the histone deacetylase enzymes being a NAD^+-dependent histone and protein deacetylase that plays an important role in several cellular and physiological processes, including an important involvement in neurodegeneration [95]. Indeed, induction of SIRT1 was shown to have a protective role in HD and SBMA models [96–98]. Resveratrol treatment in the MJD mouse model [99] was shown to improve motor and balance deficits after disease onset. This study pointed SIRT1 activation as a potential therapeutic target for MJD 94]. Resveratrol, being a multitarget compound with several neuroprotective roles, represents an interesting candidate for the treatment of MJD. Nevertheless, it is important to remember resveratrol solubility and bioavailability limitations [100], which can be solved by appropriate chemical modifications. Resveratrol was already tested in a phase 2 clinical trial in Alzheimer's disease patients and showed to be safe and well tolerated; nevertheless, the small number of participants did not allow researchers to determine whether resveratrol may be beneficial or not.

It was also stated that "More potent and bioavailable SIRT1 activators are also in development" (see *Study Results* of the NCT01504854 clinical trial), which could be useful for this and other neurodegenerative diseases.

19.3.2.4 Modulators of the Serotonergic and Glutamatergic Systems

Recently, and departing from an unbiased screening of FDA-approved small molecules, Teixeira-Castro and collaborators identified Citalopram (Selective Serotonin Reuptake Inhibitor—SSRI) as a hit compound able to modify the neurotoxic effect of mutant ATXN3 in the nematode *C. elegans*, but also its aggregation. The effect required early treatment initiation and a minimum duration. The compound was further tested in a mouse model of the disease (CMVMJD135) and shown to delay disease progression, decrease mutant ATXN3 aggregation and neuropathology. This work also demonstrated, using pharmacogenetic approaches,

that activation of the serotonergic signaling was beneficial in both animal models of MJD [101]. Intriguingly, improvement in the mouse model happened in spite of normal neurotransmitter levels at the basal state. This intriguing link between serotonin signaling and protein homeostasis has been recognized by the work of Prahlad and colleagues [102], and may imply a new perspective for usage of these established compounds in neurodegenerative diseases, including other polyQ-associated SCAs.

Although evidence for excitotoxicity is not as strong as for HD, perturbed glutamate transmission has also been proposed to play a role in MJD [62, 103, 104], namely through very intriguing links to mutant protein cleavage and aggregation. Interestingly, clinical trials using the antiglutamatergic drug riluzole demonstrated a beneficial effect in patients with different ataxias [105, 106]. Unfortunately, MJD patients were not included in these clinical trials. Considering this, and also the fact that riluzole was shown to have protective effects in cellular models of HD [107, 108], Schmidt and colleagues have studied the potential beneficial effects of riluzole in a conditional MJD mouse model [109]. Post-symptomatic chronic treatment with riluzole had no effect on motor deficits of the mouse despite the observed reduction of soluble mutant ataxin-3 protein levels. Furthermore, riluzole increased the levels of ataxin-3 aggregation. Also, and very importantly, the authors showed that treatment with riluzole decreased the Calbindin expression in Purkinje cells of the cerebellum, suggestive of possible toxicity, which might indicate that this compound might not be commendable to test in humans with MJD, or, at least, that it should be tested with caution [110].

19.4 Clinical Trials in MJD Patients

Currently, no disease modifying treatment exists for MJD. Yet, some symptomatic treatment is available, including genetic counseling, physical therapy programs, and speech and swallowing training as discussed above. The translation of findings from model systems to human patients is an important and urgent issue. Considering the lack of information on the key aspects of the pathogenic mechanism(s), the clinical and molecular heterogeneity of MJD patients and the scarcity of human biological tissues available for research, the development of translational approaches is very difficult. Still, some clinical trials have been performed for MJD (see Table 19.2). The detection of undesired side effects is also of major importance in clinical trials and must be taken in consideration. Most of the MJD clinical trials to date were performed using very few patients (less than 10) and only short-term effects were investigated, thus their outcome assessment might be compromised.

The combination of sulphamethoxazole and trimethoprim (Bactrim, a broad-spectrum antibiotic used in ear and urinary infections) was suggested to reduce disease symptoms in a small double-blind clinical trial using 8 MJD patients. The authors observed mild improvements in some of the parameters evaluated, such as hyperreflexia of knee jerks and rigospasticity of the legs in the patients treated

Table 19.2 Clinical trials performed to date in MJD patients

Therapeutic molecule	REF	Target	Design	Treatment duration (weeks)	Number of patients	Mean age (years)	Mean repeat length	Dosage	Known collateral effects	Outcome
Buspirone	Friedman et al. [121]	Serotonin 5-HT1A receptor partial agonist	Case-study	15	1	NA	NA	12.5 mg/day	Dizziness, drowsiness and headache, nausea, diarrhea, increase in appetitte	**Mild effect**; improved gait and balance; clinical rating scale for ataxia was used
Tandospirone	Takei et al. [122]	Serotonin 5-HT1A receptor partial agonist	Case-study	8	1	51	NA	30 mg/day	Dizziness, drowsiness, headache, dry mouth, insomnia	**Strong effect**; ataxia, depression, insomnia, anorexia, and leg pain were improved; ICARS and SDS scales were used
Tandospirone	Takei et al. [123]	Serotonin 5-HT1A receptor partial agonist	Open-labeled	7	10	50.6 ± 12	NA	30 mg/day 15 mg/day	Dizziness, drowsiness, headache, dry mouth, insomnia	**Strong effect**; ataxia, depression, insomnia, anorexia, and leg pain were improved; ICARS and SDS scales were used
Lamotrigine	Liu et al. [127]	Sodium channel blocking agent	Open-labeled	9	6	27	78 ± 2	25 mg twice a day	Blurred vision, changes in vision,clumsiness or unsteadiness, double vision, poor coordination, skin rash	**Positive effect**; OLST and TGI tests were performed and improved
Varenicline (Chantix)	Zesiewicz et al. [128]	Agonist of α4β2 sub-type of the nicotinic receptor	Doubled-blinded	8	20	50.6 ± 11	NA	1 mg twice a day	Abnormal dreams, change in taste, dry mouth, flatulence, headache, lack or loss of strength, nausea, sleeplessness, stomach pain, trouble sleeping, unusual tiredness or weakness	**Positive effect**; SARA scale, a timed 25-foot walk and 9-hole peg test, measurements of mood and anxiety, and adverse events

(continued)

Table 19.2 (continued)

Therapeutic molecule	REF	Target	Design	Treatment duration (weeks)	Number of patients	Mean age (years)	Mean repeat length	Dosage	Known collateral effects	Outcome
Lithium carbonate	Saute et al. [140]	Mood stabilizer (mode of action is still unknow)	Doubled-blinded	48	62	40 ± 9	75 ± 3	Weekly lithium doses were given until a target of 0.5–0.8 milliequivalents per liter (mEq/L)	Confusion, poor memory, or lack of awareness, fainting fast or slow heartbeat, frequent urination, increased thirst, irregular pulse, stiffness of the arms or legs, troubled breathing (especially during hard work or exercise), unusual tiredness or weakness, weight gain, intentional tremor	**No overall effect**; NESSCA (6) and SARA scale, 9-hole peg test, 8 m Walking Time, Click Test and PATA-rate, Composite Cerebellar Functional Score, Quality-of-Life Questionnaire, Beck Depression Inventory, Clinical Global Impression of Change
Valproic acid	Lei et al. [142]	Histone deacetylase inhibitor	Double-blinded	12	36	37 ± 6	76 ± 3	12 patients: 800 mg/day; 12 patients: 1200 mg/day	Infection, congenital anomalies, alopecia, thrombocytopenia, nausea, vomiting, abdominal pain, weakness, drowsiness, tremor, flu-like symptoms, dizziness, diarrhea, and anorexia	**Positive effect;** improvement in locomotor function given by the decrease in global SARA score which was more evident in the 1200 mg/day cohort

with Bactrim. It was also shown that the levels of biopterins and homovanillic acid were reduced in the cerebrospinal fluid (CSF) of MJD patients when compared with controls with other neurodegenerative diseases, and that the short-term treatment with Bactrim increased these levels [111]. In the same year, another double-blind clinical trial was performed using Bactrim in 8 additional patients. In this study, three parameters were evaluated: subjective performance, neurological examination and timed tests. The treatment with Bactrim again demonstrated an improvement on gait and coordination. The authors suggested that further clinical trials using Bactrim should be performed due to the promising results obtained with this small number of patients [112]. Indeed, in 2001, a third double-blind clinical trial using Bactrim was performed in 22 MJD patients. In this trial, and in contrast to previous observations, chronic treatment with Bactrim had no effect in the parameters evaluated, such as ataxia ranking scale, self-assessment score, posturography and computer assisted motor performance test of Schoppe. The visual system function and mental health were also evaluated, but no effect was observed with Bactrim treatment [113].

The progression of MJD usually confines the patients to a wheelchair and ultimately the patients will be bedridden. In this condition, and in contrast to cognitive preservation, the patients might suffer depressive symptoms. Furthermore, the serotoninergic system in the cerebellum seems to play a role in motor output, such as locomotion. Serotonergic system impairment in the cerebellum was demonstrated to induce cerebellar ataxia [114]. The selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, are commonly used in the treatment of depression and present few side-effects [115]. In fact, as discussed above, citalopram (a commonly used antidepressant) proved to ameliorate the phenotype and neuropathology of the CMVMJD135 mouse model of MJD, suggesting that serotonergic system modulation might have an important role in MJD counteracting pathogenesis. Indeed, and long before this preclinical evidence emerged, some clinical trials using antidepressants have been performed in MJD patients, however the trial design was often less than optimal for detection of an effect. Monte et al. performed an open-label trial in 13 molecularly confirmed MJD patients, and saw that after 6 weeks of treatment, fluoxetine had no overall effect on motor abilities measured by functional scales and had no beneficial effect on the other neuropsychological tests [116]. Again, the outcome of the study may have been compromised by the small number of patients and particularly by the short duration of the study.

The use of 5-HT1A agonists has been controversial for the treatment of cerebellar ataxia, but several reports have suggested the efficacy of these agonists for the treatment of MJD [117–120]. Indeed, Friedman and collaborators have shown mild effects of buspirone in one MJD patient [121]. Later, Takei et al., reported the positive effects of tandospirone, another 5-HT1A agonist, in one MJD patient, that showed improvement in ataxia, depression, insomnia, anorexia and leg pain [122]. These positive effects led the authors to pursue a larger clinical trial using 10 MJD patients. In this trial, the patients started tandospirone treatment at an initial dose of 15 mg/kg (as the previous case study) that was further increased to 30 mg/kg for

7 weeks. The patients were examined using the international cooperative ataxia ranking scale (ICARS), the total length traveled (TLT) by stabolimetry test and the self-rating depression scale (SDS). All these parameters were alleviated with tandospirone treatment. Interestingly, all the symptoms were aggravated after a transient stop of tandospirone, and improved when the therapy was restarted [123]. These results suggested that 5-HT1A agonists could be effective in MJD, although more studies need to be performed to confirm these assumptions. Interestingly, it was suggested that the effects of 5-HT1A agonists might be potentiated by the concomitant use of SSRI's (e.g. citalopram) and *vice versa* [124, 125], which could be an interesting approach considering the results of these human trials and the promising data resultant of the study showing the beneficial effects of citalopram (but also of 5-HT receptor agonists) in MJD animal models [101]

The involvement of excessive *N-methyl-d-aspartate* (NMDA)-mediated signaling in the mechanism of neuronal inclusion formation has been proposed [126]. It was recently shown that L-glutamate-induced excitation of iPSC cells of MJD patients leads to Ca^{2+}-dependent proteolysis of ATXN3 followed by the formation of insoluble aggregates. The formation of those aggregates was also dependent on Na^{+} and K^{+} channels as well as on voltage-gated Ca^{2+} channels [103]. These very intriguing observations could provide a link between excitotoxicity and ATXN3 aggregation. A pilot study was performed in 6 MJD patients using Lamotrigine (25 mg twice a day during 9 weeks), a commonly used antiepileptic drug acting as a sodium channel-blocking agent that might be related to the reduction of NMDA-induced toxicity. In this trial, the patients were evaluated in the one leg standing test (OLST) and tandem gait index (TGI). Both OLST and TGI were improved during Lamotrigine treatment, comparing the values obtained with the normal values for Chinese population. Furthermore, and given these positive results, the authors cultured lymphoblastoid cells of one MJD patient and treated those cells with Lamotrigine. Mutant, but not normal ataxin-3, was reduced with Lamotrigine at concentrations within the therapeutic range in humans. The mechanism underlying the reduction in mutant ataxin-3 levels was not investigated in this work and this effect was not confirmed in the trial subjects [127].

Recently, Zesiewicz and collaborators carried out a short-term clinical trial in 20 MJD patients using Varenicline (Chantix, 1 mg twice a day for 9 weeks) [128]. Chantix (partial agonist of the $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors) is used for smoking cessation. The rationale for this study was the fact that, although the major components of the cholinergic system seem to be spared in MJD, which may be reflected by the absence of dementia in MJD patients, the midbrain cholinergic pars compacta of the pedunculopontine nucleus suffers cell loss during disease progression [11], contributing for example to REM sleep disturbances, hence targeting the cholinergic neurotransmission could be a good approach. Chantix was also shown to be beneficial in SCA patients in previous case studies [129, 130]. In this trial, patients were evaluated at baseline and at the end of the treatment (after 8 weeks) primarily using the Scale for the Assessment and Rating of Ataxia (SARA scale). Secondary measurements consisted of a timed 25-foot walk, a 9-hole peg test, Beck depression inventory (BDI), Beck anxiety inventory

(BAI), clinical global impression (CGI), patient global impression (PGI) and the Short-Form 36 (SF36) to evaluate daily living. Chantix was able to significantly improve some subscores of the SARA scale, such as gait and rapid alternating movements. Also, the timed 25-foot walk was ameliorated by Chantix treatment, as well as the BDI score. The BDI score improved in both groups (Chantix and placebo) probably because the patients that were enrolled in the trial became hopeful regarding new treatment possibilities. A problem concerning this study was a high rate of dropout in the placebo group (4 out of 10 patients), interpreted as probably reflecting the difficulty of patients to reach the academic center. Regarding adverse events, it is possible to observe that Chantix caused, to a higher extent, gastrointestinal effects when compared to placebo. The mechanism by which Chantix improves ataxic symptoms was not evaluated in this study or elsewhere [131]. No follow up studies with larger groups of patients have been undertaken after this first promising result.

More recently, Saute and colleagues conducted a phase II clinical trial in 62 MJD patients using Lithium Carbonate. Lithium is commonly used to treat bipolar disorder, and is also used adjunctively with mood stabilizers and antidepressants to enhance, prolong and facilitate treatment response and remission of mood disorders [132, 133]. Lithium treatment was shown to have beneficial effects in several models of different neurodegenerative diseases [134–138], by the inhibition of glycogen synthase kinase-3β (GSK-3β) and autophagy activation. Importantly, however, irreversible cerebellar toxicity, leading to ataxia, nystagmus and dysarthria has also been observed due to lithium intoxication (reviewed in [139]). In this long-term clinical trial, Lithium (at therapeutic dosages of 0.5–0.8 mEq/L) was well tolerated by patients. After 48 weeks of follow-up, patients treated with Lithium did not show significant differences in disease progression, given by the results by Neurological Examination Score for the Assessment of Spinocerebellar Ataxia (NESSCA) and SARA scale. Nevertheless, the authors were able to observe that Lithium-treated MJD patients had a slower progression concerning the PATA test (word speed) and the Click test (finger-pointing coordination) as well as in the SCAFI (spinocerebellar ataxia functional index) and CCFS (composite cerebellar functional score), when compared to patients receiving placebo [133]. They suggested that larger clinical trials should be performed in order to understand the value of Lithium in the treatment of MJD.

The vast literature regarding transcription deregulation involvement in polyQ pathogenesis, led some researchers to conduct a clinical trial in MJD patients using Valproic Acid (VPA). VPA is commonly used as an anticonvulsant drug in the treatment of bipolar disorder. It has several known functions, including the increase in GABA neurotransmission, inhibition of voltage-gated sodium channels, T-type sodium channels and HDAC. In the preclinical trial field, the literature is controversial, since it was shown to be neuroprotective in a *Drosophila* MJD model [141], but showing limited therapeutic effects in a transgenic mouse model of the disease [79], as discussed above. Nevertheless, a clinical trial was recently performed in

MJD patients using VPA. In this study, Lei and collaborators used two different study designs. In the first, a randomized, open-label, dose-escalation study was performed to evaluate safety of VPA administration. In this first part of the study, it was possible to observe that VPA was safe in all the dosages tested (400, 600 and 800 mg/twice a day). In the second approach, 36 MJD patients were enrolled and randomly allocated to placebo, 800 and 1200 mg/day VPA dosing. After 12 weeks of treatment, the patients were evaluated using the SARA scale, and it was possible to observe a decrease in the total SARA score in both VPA dosages, indicating a significant improvement of the patients' motor coordination [142].

There are many concerns regarding the clinical trials performed to date in MJD: (i) the small cohorts of patients, which might be difficult to overcome due to the fact that this is a rare disorder and also the collaboration of patients might represent a problem; (ii) the clinical heterogeneity of the patients; (iii) the short-term observation of the patients, that contrasts with the slow progression of the disease (except for the Lithium Carbonate trial, which had a duration of 48 weeks); (iv) the outcomes used for ataxia measurement, which might be difficult to analyze due to the multisystem involvement in this disease; (v) the design of the studies, as randomized double-blinded trials with quantifiable ataxia scales and non-ataxia measurements should be used, which was not often the case, and (vi) the lack of useful biomarkers. Despite the existence of several scales to measure ataxia (reviewed in [143]), other non-ataxia scores should be applied to MJD patients since these patients also present non-ataxia symptoms, such as pyramidal and extrapyramidal signs, as well as peripheral findings [144].

19.5 Concluding Remarks

The search for disease-modifying therapeutic approaches for most neurodegenerative diseases has not been very productive to date; in the specific case of MJD, an important link between preclinical and clinical studies is still lacking. It is important to pursue well-designed clinical trials based on robust preclinical studies. Certainly, efforts are being made to perform good preclinical trials, and the scientific community is nowadays conducting better clinical studies with promising results for MJD. Other, non-pharmacological, disease-modifying therapeutic strategies may also be very promising.

Despite being rare diseases, MJD and other SCAs affect a large number of people worldwide. Given our current efficacy measures, large clinical trials, involving multiple centers and of long duration, are necessary which, in turn, implies high costs. Pharmaceutical companies are increasingly aware of the relevance of studying diseases of well-defined etiology, such as MJD, and their contribution could help to speed this process in a significant manner.

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