

Expert Opinion

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Dextromethorphan/quinidine: a novel dextromethorphan product for the treatment of emotional lability

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Dextromethorphan (DM) is among the most widely used, non-narcotic anti-tussives, with a predictable safety profile. In 1981, a non-opioid, high-affinity brain recognition site for DM was discovered, and since then a unique neuropharmacological profile has emerged for this 'old' drug, suggesting novel applications. However, an extensive body of research for DM alone in treating various neurological conditions has been inconsistent. This may be largely due to its rapid first-pass metabolism. DM is currently being reintroduced as the active ingredient in a novel combination product in which low-dose quinidine is added to inhibit its breakdown, elevating blood levels of DM and increasing its likelihood of reaching neuronal targets. This has opened new possibilities for therapeutic use; the best evidence at present being for neurological disorders affecting emotional control.

Keywords: σ -1 agonist, AVP-923, amyotrophic lateral sclerosis, dextromethorphan, dextrophan, diabetic neuropathy, emotional lability, involuntary emotional expression disorder, multiple sclerosis, neuropathic pain, NMDA antagonist, opioid withdrawal, pseudobulbar effect, quinidine

Expert Opin. Pharmacother. (2006) 7(18):2581-2598

1. Rationale for development of the combination product, dextromethorphan/quinidine

Dextromethorphan (DM) was first synthesised in Switzerland and subsequently patented in the USA in 1954 [101]. Its commercial use has been, more or less, restricted to the over-the-counter (OTC) market in which the drug has been available, with a brief interruption, for its antitussive and expectorant properties since 1958. As might be expected, research has historically focused on these properties.

In the 1980s, researchers at Stanford University reported that DM and its principal metabolite dextrophan (DX) exhibit antigitamatergic properties as a result of their antagonist effect on the NMDA receptor [1,2]. This led to renewed interest in these compounds and, for a time, it seemed that one of them might readily find clinical application for the treatment of a variety of neurological disorders ranging from epilepsy to stroke. An ambitious programme to develop DX as a neuroprotective drug was undertaken, and a biotechnology company was founded exclusively for the purpose of developing a potent analgesic combination of DM and morphine. Unfortunately, these efforts failed and it seemed that the research prospects for DM or DX were never going to live up to their promise.

It has recently become clear that limitations to the use of DM result primarily from the manner in which the drug is metabolised [3]. By addressing this issue, the clinical potential of DM has once again been resurrected, this time through the development of a product that combines DM with a small quantity of quinidine (DM/Q). Quinidine protects the parent drug from degradation, much the same as carbidopa protects dopamine from being oxidised before it reaches the brain.

2. Metabolism and pharmacokinetics of dextromethorphan

2.1 Dextromethorphan as a 'metabolic probe'

It is likely that more is known about the pharmacokinetic behaviour of DM than most drugs because DM has been researched extensively as a means of gaining a general understanding of drug metabolism and drug interactions [4,5]. DM was suited to its role as a metabolic probe because of its safety and high therapeutic index. Similar to a number of other drugs, including coumadin and debrisoquine, DM is metabolised by the cytochrome oxidase pathway. In the instance of DM, *O*-methylation accounts for its principal route of elimination [3]. This pathway is mediated by CYP2D6 (Figure 1).

Traditionally, the phenotypic status of subjects has been determined by administering a test dose of DM and subsequently measuring the ratio of DM to DX in urine [6]. This allows subjects to be categorised as fast, intermediate or slow metabolisers, following the arbitrary convention that a ratio of ≤ 0.3 identified a rapid metaboliser. Using this method, or determining the blood levels of DM after administration of a test dose (usually 15 – 30 mg), established that members of most populations metabolise DM extensively. At present, it is easier and less expensive to phenotype subjects using a DNA probe. This test is commercially available. Irrespective of the method, the results all lead to the conclusion that most Caucasians, ~ 93%, are rapid metabolisers of drugs using the CYP2D6 pathway. In black and Chinese populations, the number is slightly higher. These findings have obvious medical implications, leading, in some instances, to the recommendation that the blood level of a drug needs to be determined when certain medications (e.g., coumadin) are prescribed.

As genetic background may influence the disposition of a drug, it follows that interaction between drugs may also be of therapeutic concern. Usually, this has been considered as a problem to minimise or avoid. When prescribing, physicians routinely take such interactions into account.

2.2 Bioavailability of dextromethorphan

A strategy for boosting the efficacy of a drug by inhibiting the cytochrome oxidase system has only been recently considered, and the chronological development of this concept with regard to DM is reviewed here. There are a number of scenarios that make this an attractive approach, particularly for DM in which the parent compound and principal metabolite DX exhibit different receptor-binding properties. DM and DX both act as non-competitive NMDA antagonists and have affinity for σ -receptors [8,9]. However, DX exhibits higher affinity for the phencyclidine (PCP) site within the NMDA receptor-associated ion channel [10]. Conversely, DM has a higher affinity to σ -receptors compared with DX [9], and acts as a σ -1 agonist [11]. Accordingly, increasing blood levels of DM at the expense of DX offers the chance of segregating

the beneficial effects of DM from the detrimental effects of DX. This realisation led to the development of DM/Q.

During the epoch when DM was thought of primarily as an OTC product, research was also directed at increasing its bioavailability. Several controlled-release products were developed [12]. The appeal, from a commercial perspective, was that the frequency of administration of a slow-release product would offer convenience without sacrificing any benefits. There was convincing evidence that the blood levels of DM were comparable with the immediate- or slow-release formulations. However, these studies had to be conducted in patients who were intermediate or slow metabolisers, as DM is not detectable in rapid metabolisers at OTC doses. Remarkably, the blood level of DM in volunteers who were intermediate metabolisers was only 5 ng/ml after administering DM 30 mg DM every 6 h as an immediate-release formulation, or 60 mg every 12 h as a slow-release product.

A new generation of investigators, primarily neurologists, became interested in the pharmacokinetic properties of DM when it was recognised that DM and DX bind to the NMDA receptor [2]. This, in principle, offered the possibility that DM might be relegated to a new therapeutic status. In *in vitro* studies, neuroprotective properties of DM or DX were evident at concentrations as low as 10 μ M [1]. Almost complete protection was obtainable at 100 μ M. For practical purposes, this level is unobtainable in serum. However, there is evidence that DM or DX levels in the brain are greater than in the serum [13,14] and it was hoped that there might be a systemic dose at which DM or DX could be therapeutic. There was reason for encouragement when it was demonstrated in an *in vivo* model that a brain concentration of 20 μ M (6000 ng/gm) is neuroprotective.

Following up on this, a team in Boston applied a different approach to the problem that favoured DX [15]. They reasoned that because DX had been shown to be a more potent NMDA antagonist than DM, that the best therapeutic strategy was to take advantage of the bioconversion of DM to DX. To increase DX levels, they elected to treat rapid metabolisers with megadoses of DM (10 mg/kg/day). Starting with a dose of 2.5 mg/kg they slowly titrated seven amyotrophic lateral sclerosis (ALS) patients to the target dose. During the titration phase, three patients experienced hallucinations and only two patients were able to tolerate 10 mg/kg. Plasma DM was detectable in only one patient, but the authors reported that the median concentration of DX was 9.8 μ M at steady state. Considering the favourable distribution of DX to the brain, it seemed that the goal of attaining neuroprotective levels of DX in the brain was within reach. Less satisfying was the finding that cerebrospinal fluid levels of DX were ~ 5% of the plasma level. This result, of course, would be expected as DX is conjugated to glucuronide and subsequently excreted in the bile [16]. Nonetheless, the investigators enthusiastically endorsed this approach, apparently oblivious to the metabolic fate of DX in the periphery, as well as obvious tolerability issues.

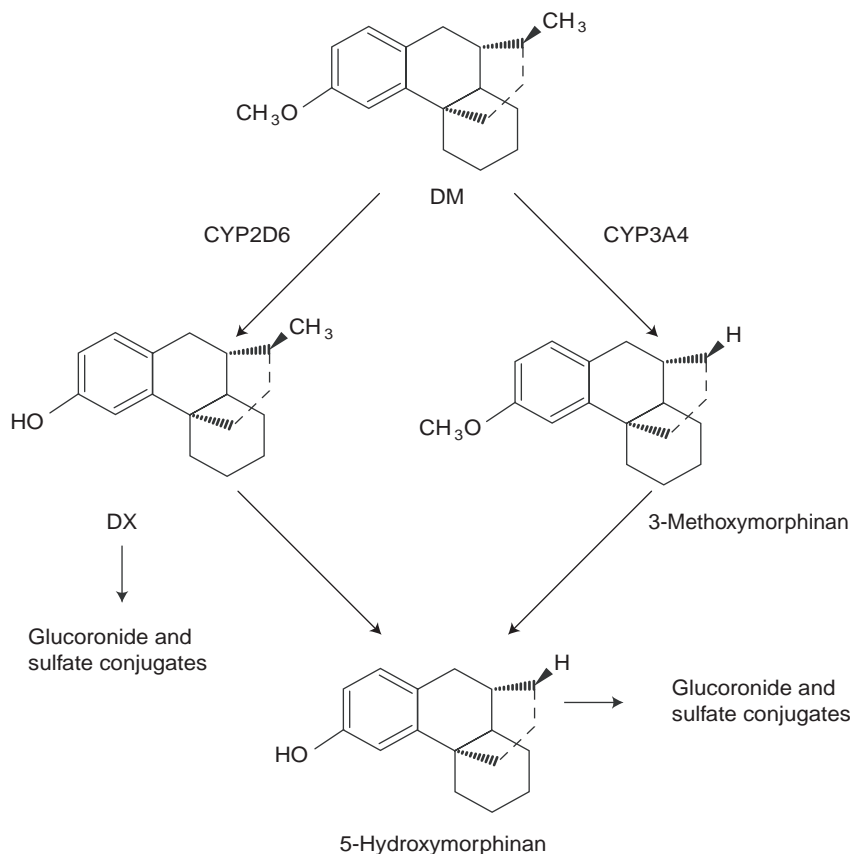


Figure 1. DM structure and metabolism. DM is a dextrorotatory enantiomer of levorphanol. DM is extensively metabolised in > 90% of the population by the hepatic CYP2D6 enzyme, which catalyses the O-demethylation of DM to its main metabolite DX. An alternate pathway is mediated primarily by CYP3A4 and N-demethylation to form 3-methoxymorphan.

Information from [3,7].

DM: Dextromethorphan; DX: Dextrorphan.

An arguably more refined approach adopted a therapeutic strategy that focused on DM, in the hope of minimising the side effects of treatment. By the time these studies were undertaken, it was apparent that excessive blockade of the NDMA receptor was associated with unacceptable clinical effects similar to those observed with PCP. One such clue came from studies involving MK801, a non-competitive NMDA antagonist, which proved to be poorly tolerated in Phase I studies and never went into clinical trials. Furthermore, the effort to use DX as a putative treatment for stroke had a similar negative outcome [17]; thus, the future, if there was to be one, lay with DM.

3. The role of quinidine in enhancing the bioavailability of dextromethorphan

In the mid-1980s, a number of investigators reported that quinidine was a potent inhibitor of drug metabolism. Inaba *et al.*, using liver microsomes, demonstrated that quinidine was 10-fold more potent than any other drug tested [18].

Subsequently, several researchers reported that quinidine significantly impacted the degradation of debrisoquine and sparteine in patients [18].

To determine the effect of quinidine on the metabolism of DM, a group of ALS patients who might potentially benefit from treatment with a neuroprotective drug were studied [19]. As quinidine has traditionally been used as an antiarrhythmic drug at doses ranging from 600 to 1600 mg/day, it was hoped that its effect on the cytochrome oxidase system would be evident at a lower dose, one that would be unlikely to compromise cardiac function. Accordingly, studies were undertaken with quinidine 150 mg, administered daily as a divided dose for 1 week. Subsequently, subjects were phenotyped with a DM challenge given as either a single 30 or 60 mg dose. Urine was collected over the following 8 – 10 h, and frozen for later analysis. All 13 subjects were converted from rapid to slow metabolisers (Figure 2).

Next, the relationship between the dose of DM and the mean plasma levels was determined [19]. Subjects were once again stabilised on quinidine (75 mg b.i.d.) for 1 week.

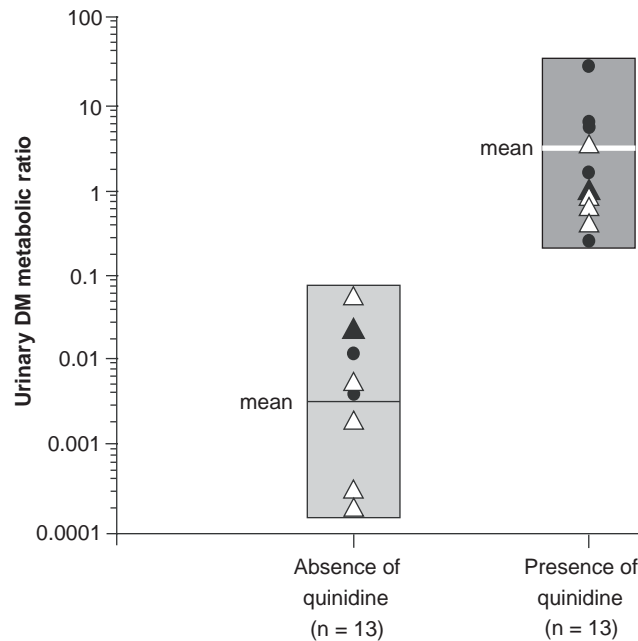


Figure 2. The DM urinary metabolic ratios in 13 efficient metabolisers before and after 1 week of treatment with quinidine 150 mg/day. Subjects were challenged with either DM 30 mg/day (n = 6) or 60 mg/day (n = 7).

DM: Dextromethorphan.

Subsequently, the dose of DM was gradually increased at 1 week intervals from a minimum of 15 mg/day to a maximum of 60 mg b.i.d. At the end of each week, a blood sample was collected 2 – 3 h after the last dose of DM in that dosing interval. The results were striking: there was an almost linear relationship between the dose and the plasma levels.

Additional insight into the kinetics of this inhibition was provided by the eloquent studies of Pope *et al.*, who established the minimum dose of quinidine needed to maximally block CYP2D6 [2]. The investigators began by determining the effect of an increasing quinidine dose on the metabolism of a fixed DM dose in a group of rapid metabolisers. After a single dose of quinidine 75 mg, > 60% of subjects were converted to slow metabolisers. Further studies showed that five doses of quinidine 25 mg b.i.d. over 3 days converted all subjects. Even subjects receiving as little as 2.5 mg quinidine b.i.d. over 7 days had a 12-fold increase in the mean peak plasma level of DM. It was thus established that a dose of quinidine as low as 25–30 mg b.i.d. is adequate to maximally suppress *O*-demethylation of DM at steady state; higher doses do not further increase its systemic availability (Figure 3). These findings provided the basis for the combination of fixed doses selected for DM/Q.

Knowledge of the pharmacokinetic behaviour of DM led to a paradigm shift, which allowed for a predictable dosage regimen. By blocking the degradation of DM, it is now possible to prescribe a standard dose of DM to any patient, with the expectation that the serum levels will fall

into a predictable range. Clinicians were left to determine if the combination product (DM/Q) is of therapeutic benefit, and it was not long before this became evident.

4. The combination product dextromethorphan/quinidine and receptor pharmacology

DM/Q is a capsule containing a fixed combination of dextromethorphan hydrobromide (DM 30 mg) and quinidine sulfate (30 mg) for oral administration. DM is the therapeutically active ingredient. The low dose of quinidine serves to maximally inhibit the rapid first-pass metabolism of DM, thereby increasing its systemic availability and potential therapeutic utility [3,19]. Importantly, the daily quinidine dose administered as part of DM/Q therapy (30 mg every 12 h) is 10- to 25-times lower than the 600 – 1600-mg/day dose routinely used to treat cardiac arrhythmias [20].

DM/Q is believed to exert its therapeutic effects by a novel means, possibly involving the interaction of several receptors (Figure 4). Current bias is that DM is principally acting as a σ -1 receptor agonist [11]. However, it is also a low-affinity, uncompetitive NMDA receptor antagonist [1,10,21,22], and seems to act as a weak serotonin re-uptake inhibitor [23,24]. σ -Receptors modulate neurotransmitter release [8], and DM has been shown to decrease glutamate release *in vitro* [25]. DM also blocks NMDA responses to glutamate [21]. σ -1 Sites are particularly concentrated in the brainstem and cerebellum [11,26], and DM has been shown to preferentially bind to these brain regions in animals [1,27].

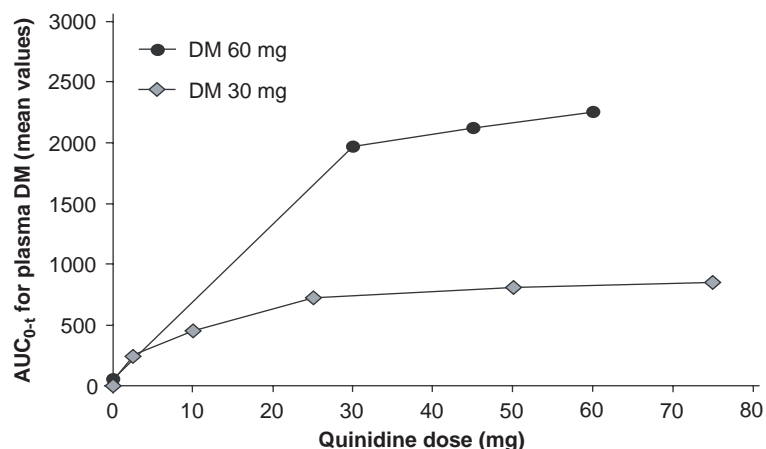


Figure 3. Quinidine dose effects on systemic levels of DM at steady state. Steady-state was attained after 1 week of twice-daily dosing with DM/Q. The effects of increasing quinidine were not different with doses > 25 mg, whereas lower doses showed a dose-related increase in plasma DM concentrations. Points represent a mean of seven or eight subjects. AUC values (ng•h/ml) were determined 8 h after dosing with DM 30 mg or 12 h after dosing with DM 60 mg.

Information from [3].
DM: Dexamethorphan.

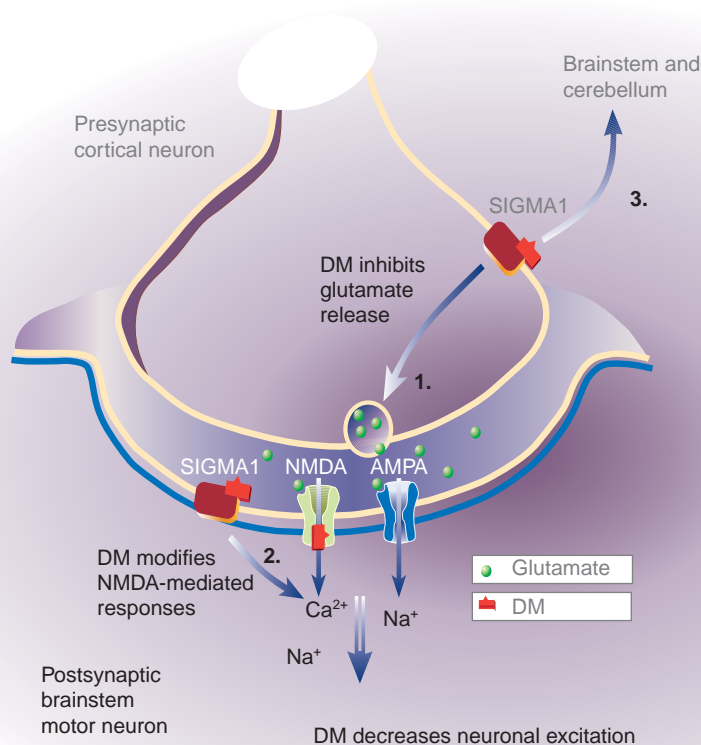


Figure 4. The mechanisms of action of dextromethorphan on emotional control are likely to be multifactorial, involving several neurotransmitters. Although unproven, there is reason to believe the main site of action is on the brainstem and cerebellum, areas of the brain decorated with σ -receptors.

DM: Dexamethorphan.

5. Dextromethorphan/quinidine for the treatment of emotional lability associated with neurological disorders

5.1 Description of emotional lability, an unmet medical need

Emotional lability, manifested by the occurrence of inappropriate tearfulness, laughter and anger, is a common disorder associated with kindred conditions. It was recognised by Charles Darwin in 1872, who wrote that, '*Certain conditions that cause wasting such as senility have a special tendency to evoke weeping*' [28]. The condition occurs secondary to neurological disease or injuries including ALS [29], multiple sclerosis (MS) [30], stroke [31], traumatic brain injury [32], Parkinson's disease [33] and dementia, including Alzheimer's disease [34]. The disorder can be severe and persistent [35]. It may be potentially debilitating to patients in social and vocational settings [36], and it can add to caregiver burden [37,38]. Other terms used to refer to this disorder include pseudobulbar affect (PBA), pathological laughing and crying (PLC) and emotional incontinence [35]. In the belief that all of these terms are confusing or objectionable, the more inclusive term 'involuntary emotional expression disorder' (IEED) has been proposed. As this terminology has not yet been widely adopted, and because of the time-honoured use of many of these terms in the literature, these terms will be used interchangeably in this review.

There is consensus that emotional lability is caused by structural damage to the brain, that its hallmark symptoms are episodes of crying or laughing, and that these episodes are sudden, involuntary, difficult to control, disproportionate to provoking stimuli and labile [35,39]. Lack of agreement on other defining features and clinical presentations, particularly on whether or not the loss of control of the motor expression of emotion is meaningfully related to the mood of the patient [35,39], may, in part, account for the plethora of terms for the disorder. These distinctions are further blurred in the clinical setting when patients exhibit loss of emotional control that goes far beyond the common understanding of the behaviour usually associated with emotional lability. In these instances, labile anger may, for example, predominate with the result that physicians may not even consider the diagnosis of emotional lability. Surprisingly, some physicians trivialise the disorder, one offering the opinion in a recent publication that physicians '*Concentrate our efforts on the identification and development of treatment for major symptoms, such as spasticity*' [40]. Unlike spasticity, which is adaptive and may provide an important splinting effect in the instance of a weak limb and thus may not require treatment, emotional lability provides no apparent benefit. When it interferes with the quality of life (QoL), good medical practice dictates it be treated [41].

Although common, emotional lability is under-recognised and undertreated [36]. The disorder is often mistaken for depression [42]. Furthermore, there is no approved

pharmacotherapy with a specific indication for emotional lability. Antidepressants and dopaminergic agents have been used to treat the disorder with partial success [43]. Most studies have been small comparative trials, which have demonstrated mixed results for tricyclic (TCA) [44] and selective serotonin re-uptake inhibitor (SSRI) [45] antidepressants. Not all patients respond to treatment with antidepressants [46] and/or cannot tolerate side effects due to comorbidities. TCAs are associated with a high incidence of adverse events (AEs), including anticholinergic effects (e.g., memory deficits) [47], that are particularly problematic in the elderly. None of these agents have been proven effective using standardised, validated measurement scales [39] and long-term safety monitoring. As a result, even severe cases frequently remain untreated [36].

5.2 Structural damage to the brain underlying emotional lability

The exact mechanisms underlying emotional lability are unknown. It is proposed that the disorder is a disinhibition or 'disconnection' syndrome [48] resulting from lesions that interrupt: i) voluntary, inhibitory control of motor cortex over bulbar effector regions that organise facio-respiratory responses constituting crying/laughter [49]; or ii) cerebellar communication with higher association cortex (e.g., limbic and prefrontal cortex) via the pons, thereby disrupting cerebellar adjustment of crying/laughing to the appropriate cognitive and social context (**Figure 5**) [50].

In the first scenario, proposed in 1924 by Kinnier Wilson, weakened cortical inhibition of a presumed laughing/crying centre in the upper brainstem is suggested to 'disinhibit' or 'release' involuntary, emotionally driven crying/laughter (pathways not shown) [49]. The contemporary view, proposed by Parvizi *et al.* in 2001, assumes a disconnection of neuronal centres that process contextual information related to emotion [50]. In this scenario, emphasis is placed on the cerebellum, which is postulated to exert a regulatory effect on cortical association areas involved with emotional contexts. If these circuits are disrupted, the cerebellum operates on the basis of incomplete information, the outcome being exaggerated or inappropriate emotional displays.

Further support for the idea that damage to fronto-temporal-subcortical circuits may underlie emotional lability comes from studies of ALS patients. Up to 50% of ALS patients suffer from emotional lability [29], and McCullagh *et al.* demonstrated that ALS patients with emotional lability were impaired on the Wisconsin Card Sort Test, an index of prefrontal cortical function [51]. Moreover, Lomen-Hoerth *et al.* suggested that frontal executive deficits are present in half of ALS patients, many of whom meet strict research criteria for frontotemporal lobar dementia [52].

5.3 Neurotransmitters involved in emotional lability

The active ingredient of DM/Q is DM, a σ -1 receptor agonist [11]. σ -1 Sites are particularly concentrated in the

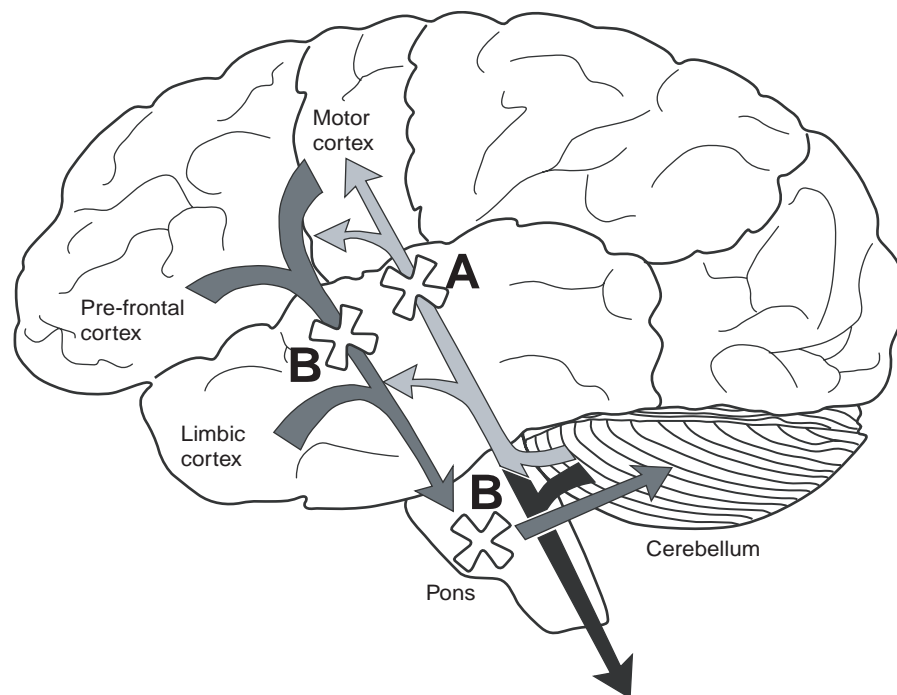


Figure 5. Emotional lability is caused by structural damage to brain networks underlying the motor expression of emotion.

The disorder is proposed to be a 'disinhibition' or 'disconnection' syndrome, resulting from lesions to two main brain pathways: A) corticobulbar degeneration that effectively releases cortical inhibition of brainstem centres that organise laughing/crying responses and B) cerebro-ponto-cerebellar lesions that interrupt cerebellar communication with higher association cortex (e.g., limbic and prefrontal cortex), thus disrupting cerebellar adjustment of crying/laughing to the appropriate situation. Large X symbols indicate potential lesions along these pathways.

Information from [35,39,49,50].

brainstem and cerebellum, among other regions [11]. DM has been shown to preferentially bind in the brainstem and cerebellum [2,27], regions also thought to be involved in the control of emotional displays [49,50]. The mechanism by which DM/Q relieves symptoms of emotional lability is unknown. However, based on the outlined evidence, its therapeutic effect may depend on its ability to act as a σ -receptor ligand and to modulate excitatory, glutamatergic signalling. Assuming this to be the case, dysregulation of σ -receptor function may also play a role in the aetiology of emotional lability.

5.4 Measuring emotional lability

Two objective and validated instruments exist to assess emotional lability: the Pathologic Laughter and Crying Scale (PLACS) and the Center for Neurologic Study-Lability Scale (CNS-LS). The PLACS was developed by Robinson *et al.* and validated in a population of stroke patients [44]. It is administered by a health professional, who interviews the patient and notes responses. For the purpose of clinical trials, it was thought that a self-assessment scale might be advantageous, as it would not be necessary to establish the correlation between the results of raters at different facilities. This led to the development of the CNS-LS by Moore *et al.*,

the first self-reported measure of emotional lability validated in both an ALS [53] and MS [54] population, and the focus of this discussion.

In its simplest form, the CNS-LS is a seven-item scale assessing subjects' perception of their emotional lability as manifested by tearfulness and laughter. An auxiliary subscale for anger and frustration, added features of IEED, has also been developed and validated for use in ALS [53]. The scale has proven to be a robust end point in clinical trials, but its use has primarily been as a research tool. It should be equally valuable in a clinical setting to facilitate the diagnosis of emotional lability and as a means of monitoring the response to therapy (Box 1) [48].

The CNS-LS reliably quantifies perceived aspects of emotional lability, including its frequency, intensity, lability, degree of voluntary control and inappropriateness to context. It consists of two subscales: one for laughter (four items) and one for tearfulness (three items). It also includes an auxiliary subscale measuring labile frustration, anger and impatience. Each increase of one point in the CNS-LS score corresponded to ~ 12 and 11% higher episode rate in ALS [48] and MS [77] patients, respectively.

Development of the CNS-LS was initially undertaken in a population of ALS patients [53]. At the outset, 10 patients

Box 1. Center for Neurologic Study-Lability Scale (CNS-LS).

- Self-report measure of emotional lability validated in ALS and MS
- One-point increase = 11 – 12% greater episode rate
- Sample questions from seven-item scale:
 - = I find myself crying very easily
 - = I find that even when I try to control my laughter I am often unable to do so
- Respondents indicate on a five-point scale how often they experience symptoms described in each item:
 - 1 = Never
 - 2 = Rarely
 - 3 = Occasionally
 - 4 = Frequently
 - 5 = Most of the time

ALS: Amyotrophic lateral sclerosis; MS: Multiple sclerosis.

exhibiting emotional lability were interviewed by a psychologist for the purpose of generating items for a questionnaire that reflected the patients' feelings, thoughts and behaviours related to their disorder. Five neurologists, who were familiar with emotional lability associated with neurologic disorders, condensed the extensive list to 57 items. The most relevant of these were selected via feedback from 99 ALS patients who were asked to score each item for significance on a five-point scale. Using principal components and Scree slope analysis, three underlying factors were identified. The first factor consisted of eight items that assessed labile frustration, impatience and anger. Factor two contained four questions that dealt with pathological laughter, and the final factor included three questions that assessed labile tearfulness. Factors two and three together totalled seven items for laughter/crying. To gain insight as to the construct validity of the CNS-LS, the results were compared with those obtained on the Affective Lability scale and the Beck Depression Inventory. Scores for the seven-item CNS-LS were closely associated with the former, whereas the three questions probing pathological tearfulness correlated with the latter. In short, the seven items of which the short version of the CNS-LS consists were shown to be valid measures of emotional lability.

To assess criterion validity, the CNS-LS was next administered to 77 ALS patients who were independently evaluated by a neurologist to establish a diagnosis of emotional lability. Commonly accepted criteria were used to establish the diagnosis, namely the occurrence of inappropriate tearfulness and/or laughter. This was often noted on examination, but the medical history supplied by the patient and caregivers was sufficient grounds to make a diagnosis. A total of 46 patients were diagnosed as exhibiting emotional lability. CNS-LS scores were significantly higher in the emotionally labile group (18.46

± 6.32 , mean \pm s.d.) than in the non-labile group (10.19 \pm 3.45, mean \pm s.d.). Ultimately, a CNS-LS score of 13 was selected as a cut off for making the diagnosis of emotional lability associated with ALS.

The CNS-LS was further validated in a parallel study of MS patients conducted at seven centres [54]. Out of 90 MS patients selected to participate, 50 were physician diagnosed with emotional lability. In this population, it was determined that a score of ≥ 17 on the CNS-LS identified IEED with a sensitivity of 0.94 and a specificity of 0.83. From the time of its description by Charcot, it has been known that MS patients tend to minimise their disability. He referred to this as '*belle indifférence*'. This may account for the difference in the CNS-LS scores in patients with emotional lability who have MS versus those who have ALS.

5.5 Distinction between emotional lability and depression

Emotional lability may coexist with depression in some patients, confounding differentiation of the two disorders. MacHale *et al.* found poststroke emotional lability to be significantly associated with depression ($p < 0.0001$), with 62% of patients meeting criteria for a depressive illness [56]. Similarly, House *et al.* reported that poststroke emotionality is associated with symptoms of a more general mood disturbance, as evidenced by higher Beck Depression Inventory and present-state examination scores [31].

Although the principal aetiologies of emotional lability and depression seem dissimilar, this difference is also ambiguous. The primary cause of emotional lability is thought to be structural damage to the brain [35], whereas that of depression is believed to be a metabolic and functional monoamine disturbance [57]. Nevertheless, a dysregulation of serotonin neurotransmission has been implicated in emotional lability [58]. Moreover, structural neuroimaging methods have demonstrated volume reductions in several brain regions of patients with major depressive disorder, including the prefrontal cortex, the amygdala and components of the basal ganglia [59]. Some of the same regions have been implicated in emotional lability [35,60]. Therefore, a clear discrimination of the two disorders is not possible based solely upon aetiology.

For these reasons, as well as common symptomatology, emotional lability is often mistaken for depression and not properly treated. Crying spells are a clinical symptom of depression [61] and can mimic the crying episodes that are hallmark characteristics of emotional lability. The context in which the symptoms arise, and their features, may help to clarify the diagnosis [35]. For example, appropriate (mood-congruent) crying has been more commonly observed in psychiatric disorders, whereas dissociated (mood-incongruent) crying is more common in neurological disorders [42]. Nevertheless, Green *et al.* demonstrated that the presence of neurological disease is vastly underestimated by referring physicians [42]. Out of 46 patients referred to a psychiatric consultation service with a presumed diagnosis of depression due to prominent crying, 76%

had a neurological disorder and just 20% had a psychiatric disorder only.

Despite the blurred distinctions, there is convincing evidence that emotional lability and depression are separate disorders, and that validated measurement scales can facilitate this distinction. First, emotional lability may be found independent of depression. Robinson *et al.* demonstrated that scores on the PLACS were not significantly correlated with Hamilton Rating Scale for Depression (HRSD) scores in stroke patients [44]. Furthermore, prevalence statistics for ALS patients suggest that emotional lability can occur without depression in this population. Although 40 – 50% of ALS patients, many with bulbar symptoms, suffer from emotional lability [29,62], only 11 – 22% of ALS patients are depressed [63,64]. A recent study of a large ALS population examined this issue more directly, and the findings provide convincing evidence that the two are discrete illnesses [65]. This analysis was part of a Phase III clinical trial designed to evaluate DM/Q for the treatment of emotional lability in ALS (n = 181), and was, therefore, not specifically designed as a demographic study. However, baseline screening for the trial provided a unique opportunity to evaluate the two affective disorders in ALS, using the CNS-LS and HRSD. The findings show that emotional lability occurs independently of depression (Figure 6).

5.6 Clinical efficacy of DM/Q in the treatment of emotional lability in amyotrophic lateral sclerosis

5.6.1 Background

ALS is the most common motor neuron disorder, and is frequently associated with emotional lability. In ~ 50% of cases, the disease runs its fatal course within 3 years [66]. The brunt of the pathological process is borne by large motor neurons in the spinal cord and brainstem. This accounts for the weakness and wasting that are characteristic of the disease. Cortical spinal pathways descending from the motor and association cortices are also involved, usually bilaterally. This further compromises motor function at the spinal level, causing stiffness and spasticity. In addition, cortico-spinal tract involvement can compromise bulbar functions, such as speech and swallowing, and result in emotional lability. As shown above, corticobulbar degeneration can effectively release cortical inhibition of brainstem centres that organise laughing/crying responses [49]. Loss of control of emotional expression is a common occurrence in the ALS population as a whole, and patients with bulbar involvement are more likely to exhibit symptoms. In one study, the prevalence of emotional lability was reported to be ~ 50% [29]. The prevalence was found to be markedly lower in another analysis, and in this case a much lower percentage of patients had bulbar signs [67]. In the author's opinion, the variance is also, in part, attributable to methodological differences. For example, some surveys rely on unstructured interviews, rather than validated measurement scales, and certain patients with overt emotional lability deny the problem.

There is no effective treatment for ALS and, consequently, the mainstay of therapy is symptomatic management [68].

Riluzole, an inhibitor of glutamate release and the only agent presently approved for clinical use, only extends survival by a few months [69]. Most efforts are thus aimed at optimising QoL. There is compelling evidence that treatments such as gastrostomy and ventilatory support can favourably affect patient outcome. Moreover, the successful palliation of emotional lability with DM/Q in an ALS population, as summarised here, is another example of the powerful impact of symptomatic care on well being [70].

5.6.2 Study design

The first Phase III efficacy trial of DM/Q was conducted at 17 academic centres across the US [70]. Patients were enrolled between January 2001 and April 2002. Study inclusion required a diagnosis of probable or definite ALS according to the El Escorial (World Federation of Neurology) criteria. Along with exhibiting a diagnosis of emotional lability, patients were required to attain a CNS-LS score of ≥ 13 at screening. Patients were excluded if they were depressed as determined by their HRSD score. Participating patients agreed not to take prohibited medications such as antidepressants or medications that might affect CYP2D6 or -3A4. Based on the results of CYP2D6 genotyping, subjects were classified according to predicted phenotype as poor, intermediate, extensive or ultra-rapid metabolisers.

The study was designed to test each of the components (DM and Q) against the combination. Accordingly, patients were treated with DM/Q, DM alone or quinidine alone, with twice as many subjects receiving DM/Q as either DM or quinidine (2:1:1 ratio). Capsules, all identical in appearance, contained DM 30 mg plus quinidine 30 mg (DM/Q) or 30 mg of each separate component. The study was randomised by centre, and randomisation was blocked to ensure approximately equal representation within treatment centres using a computer algorithm.

Capsules were taken orally by the patients twice daily (every 12 h) for 28 days. Patients were asked to chronicle in a daily diary the number of laughing and crying episodes and the AEs experienced.

5.6.3 Evaluation

Patients were assessed prior to dosing (baseline) and on days 15 and 29. On each of these days, subjects completed the CNS-LS questionnaire and visual analogue scales (VAS) assessing QoL and quality of relationships (QoR). The HRSD was administered at the beginning and end of the study. Subjects who discontinued early, returned as soon as possible to complete a 'final visit'. Safety was evaluated by monitoring AEs, physical examination results, vital signs, resting ECGs, and clinical laboratory values for serum chemistry, haematology and urinalysis. Blood samples were taken following the last dose to determine concentrations of DM, its metabolite DX and quinidine.

The primary efficacy variable was the change from baseline in the CNS-LS score. Secondary end points were: i) the

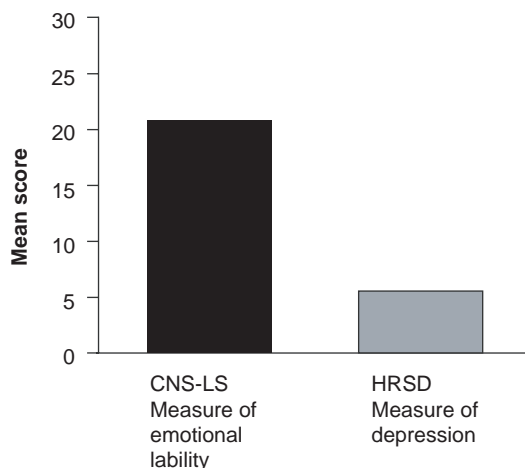


Figure 6. Emotional lability exists independently of depression in ALS patients, supporting the idea that emotional lability and depression are separate disorders. Mean CNS-LS scores (~ 21) and HRSD scores (~ 5) measured in screened patients (n = 181) indicate that subjects within this large ALS group commonly had emotional lability, but were generally not depressed. CNS-LS scores ≥ 13 indicate that the patient suffers from symptoms of emotional lability. HRSD scores ≥ 16 are consistent with moderate or greater depression. Furthermore, there was no significant correlation between the CNS-LS and HRSD scores ($r = 0.033$). Only 2 out of 181 screened patients had moderate depression. These patients were not randomised for treatment.

Information from [65].

ALS: Amyotrophic lateral sclerosis; CNS-LS: Center for Neurologic Study–Lability Scale; HRSD: Hamilton Rating Scale for Depression.

number of laughing or crying episodes per week recorded in patient diaries; and ii) change from baseline in QoL and QoR scores. All efficacy variables involving a change were determined as the baseline score subtracted from the mean of the scores on days 15 and 29. Slow metabolisers were omitted from the intention-to-treat (ITT) efficacy analysis.

Comparisons were made between DM/Q and each constituent. Changes from baseline in CNS-LS, QoL and QoR scores were assessed using linear regression models. Secondary efficacy variables were also combined and analysed simultaneously by using the O'Brien rank sum method, to account for multiple comparisons of end points. AE comparisons used the Fisher exact test.

5.6.4 Results

Of the 140 randomised patients, 11 were identified by genotyping to be poor metabolisers of DM. Of the remaining 129 ITT patients, 125 were evaluable in that they completed at least one of the scheduled on-study evaluations, and 108 (84%) completed the study. The ITT cohort included 80 men and 49 women. The mean age was ~ 55 years (range 33 – 82 years), and most were white. The CYP2D6 genotypes in each randomised treatment group were similar ($p = 0.94$).

5.6.5 Inhibition of DM metabolism

The mean DM plasma concentration was 18-fold higher in the DM/Q group (96.4 ± 46.7 ng/ml, mean \pm s.d., $n = 35$) than in the DM group (5.2 ± 5.0 ng/ml, $n = 23$), and the mean concentration of DX was 3.3-fold lower in the DM/Q group (89.5 ± 52.3 ng/ml) than in the DM group ($295.9 \pm$

143.2 ng/ml). These differences between DM/Q and the DM-only group were significant for both DM and DX ($p < 0.0001$). Analysis of quinidine revealed a median level of 150.0 ng/ml in the DM/Q group (range < lower limit of quantification to 2210 ng/ml; $T_{\max} = 2$ h).

5.6.6 Improvement of CNS-LS score

The primary efficacy end-point analysis (ITT) cohort included 125 patients. The unadjusted decrease in CNS-LS in the DM/Q group was greater (7.39 ± 5.37 , mean \pm s.d.) than that in the DM group (5.12 ± 5.56) or the quinidine group (4.91 ± 5.56).

For statistical comparison, the difference in mean CNS-LS improvement was adjusted for two important, prospectively defined covariates: baseline CNS-LS score and study centre. This accounted for greater improvements, regardless of assigned treatment, observed in patients with higher baseline CNS-LS scores. The adjusted mean reduction of CNS-LS in the DM/Q group was 3.29 points greater than in the DM group ($p = 0.001$), and 3.71 points greater than in the quinidine group ($p < 0.001$).

5.6.7 Decreased laughing/crying episodes

Diary records were evaluated for the number of crying episodes, laughing episodes and laughing plus crying episodes per week. Episode rates were highly variable. A single outlier in the DM group reported 10-times more episodes (primarily laughing) than any other patient in the study, an average of > 100 episodes/day. Omitting this outlier from the analysis, the average episode rate recorded in the DM/Q group was

1.9-times lower than in the DM group ($p = 0.004$) and 2.1-times lower than in the quinidine group ($p < 0.001$).

To help quantify and understand how changes in CNS-LS score compare to the number of episodes, the 'effect' of a one-point change on the CNS-LS score on the episode rate during the previous 2 weeks was estimated. For each one-point increase in CNS-LS score, the average episode rate increased 12%. Thus, the ~ 3.5 -point decrease in CNS-LS score with DM/Q compared with its constituents corresponds to a 50% decrease in episode rate. This is true for both laughing and crying episodes.

5.6.8 Improved QoL and QoR

The adjusted mean changes in VAS scores for QoL and QoR in the ITT group treated with DM/Q were greater than those in either of the other two groups at all time points examined. The significance level of improvement increased with longer duration of drug treatment.

To account for multiple comparisons, all secondary efficacy variables were combined and analysed using the non-parametric method of O'Brien. The results showed that subjects treated with DM/Q had a reduction in laughing/crying episodes and improved QoL and QoR scores relative to subjects treated with DM ($p = 0.004$) or quinidine ($p < 0.001$).

5.7 Decreased anger, frustration and impatience

Outbursts of anger, frustration, impatience and irritability can be part of the spectrum of labile emotions manifested as IEED, particularly in some populations, for example patients with traumatic brain injury or Alzheimer's disease [39,42,71]. These mood changes may also be associated with laughing or crying, the hallmark symptoms of the disorder.

In a clinical trial using a combination of DM and quinidine for emotional lability [72], the study that provided the rationale for the development of DM/Q, treatment effects on anger, frustration or impatience were also measured with the CNS-LS auxiliary subscale. This single-centre trial included mostly ALS patients and had a randomised, double-blind, placebo-controlled, cross-over design. Treatment lasted for 1 month with drug and 1 month with placebo. A 1-week washout period separated the trial limbs. The primary efficacy end point was improvement from baseline in total score on a 65-item self-report measure of total labile affect, which was later condensed and validated as the CNS-LS.

The combination of DM (30 mg) and quinidine (75 mg), DM/Q, given twice daily was found to significantly suppress IEED versus placebo ($p = 0.0001$) [72], including aspects of anger, frustration and impatience [73]. Therapy resulted in an $\sim 25\%$ improvement from baseline in the auxiliary subscale score (-24.9 ± 22.1 mean \pm s.d. ; $p = 0.0019$). Although labile anger and frustration are not always components of IEED, these findings suggest that DM/Q may help to relieve such episodes when present, in addition to reducing laughing or crying.

5.8 Clinical efficacy of dextromethorphan/quinidine in the treatment of emotional lability in multiple sclerosis

5.8.1 Background

MS is one of the most debilitating diseases of adults, affecting $\sim 300,000$ persons in the US [74]. It is more common in women, in contrast to ALS, which affects more men. Unlike ALS, the disease is chronic so that those afflicted live relatively long lives and must deal with their disabilities for a lifetime. The hallmark of MS is demyelination that results in the formation of plaques. The disease usually proceeds in a relapsing and remitting fashion. Over time, there is an increased disability due to the destruction of white matter and its underlying axons. Overall, $\sim 40\%$ of MS patients report disabling pain that interferes with their daily activities [75]. A typical patient with relapsing/remitting MS will likely need ambulatory assistance ~ 15 years into their illness. At about this time, the disease will often change character, seeming to progress inexorably without any dramatic setbacks. As the disease advances, it is often accompanied by cognitive changes and the occurrence of emotional lability [30].

Surveys suggest that emotional lability occurs in $\sim 10\%$ of patients [30]. Interestingly, inappropriate laughter seems to be more common in MS patients than in most other diseases [55]. In MS, as in ALS, emotional lability often occurs with corticobulbar degeneration. The pattern of cerebral demyelination most commonly observed in MS patients may interrupt corticobulbar circuitry [30].

There is no cure for MS. Immunomodulatory treatments, primarily the use of IFNs and copolymer-1, are the mainstay of therapy [76]. In general, these medications decrease the occurrence of relapses and lessen the impact of the disease with time. However, symptomatic treatment remains an essential component of care. Recently, DM/Q has been shown to relieve emotional lability in an MS population, thereby improving the QoL of patients [77].

5.8.2 Study design

The pivotal MS treatment trial for DM/Q was conducted in the US and Israel [77]. It was similar to the study conducted with ALS patients, but differed in important ways. The combination product was tested against a placebo rather than against its components, and the trial was conducted for 3 months versus the 1-month ALS trial. Subjects were required to meet the International Panel (McDonald) criteria for a diagnosis of MS, and they had to have a clinical diagnosis of emotional lability and a CNS-LS score of ≥ 13 at study outset. Subjects also completed a pain intensity rating scale (PIRS) at all clinic visits, for which they indicated the amount of pain experienced within the previous 24 h using a five-point valuation. In this regard, it is important to note that the study was not powered to observe an effect on pain, and there was no entry requirement that subjects must report pain.

Concomitant use of immunomodulatory therapies was permitted, assuming patients were on an established regimen. As MS exacerbations or treatment with corticosteroids could confound the results of the efficacy assessments, patients who experienced a relapse were withdrawn. The procedures for the final study visit were conducted at the time of withdrawal. Concurrent pain medications were allowed during the study (e.g., fentanyl, gabapentin, lidocaine, oxycodone, tramadol, hydrocodone and OTC analgesics).

Eligible patients, randomised in a 1:1 ratio to receive capsules containing either DM/Q (DM 30 mg/quinidine 30 mg) or placebo, took study medication every 12 h for 85 days. As in the ALS study, extensive clinical and laboratory tests were performed serially to establish the efficacy and safety of treatment.

5.8.3 Evaluation

The statistical analysis was similar to that in the ALS study. The differences between baseline scores (day 1) and the average of the four scores on days 15, 29, 57 and 85 were compared. Non-missing scores were averaged when data for any visit was missing. All patients who took study medication were included in the analysis according to their assigned treatments. A sample size calculation determined that 48 patients in each randomised treatment group would be sufficient to detect a difference of three points in the CNS-LS score with 90% power.

5.8.4 Results

A total of 150 patients were randomised to treatment, approximately half in the DM/Q group and the remainder in the placebo group. Enrollment began in December 2002 and ended in June 2004. An equal number of patients discontinued in each arm of the trial, 21 in both the DM/Q and placebo groups. Slightly more of these discontinued due to AEs in the treatment group (14.5%) compared with the placebo group (10.8%), excluding MS exacerbations.

The DM/Q and placebo groups were similar in baseline characteristics, including frequencies of CYP2D6 phenotypes. Baseline PIRS scores were comparable, indicating mild/moderate pain. Both groups similarly and frequently used analgesics.

5.8.5 Improvement in primary and secondary end points, including an evaluation of pain

As in the ALS study, reduction in the CNS-LS score was the primary efficacy end point. Treated patients had a greater decrease in CNS-LS score compared with those who received placebo ($p < 0.0001$); on average, the adjusted mean improvements for patients on DM/Q was more than twice as great as for placebo patients. The improvements in CNS-LS score were also compared for each visit separately (Figure 7). At each time point, subjects receiving DM/Q had a greater decrease in CNS-LS score than those receiving placebo ($p < 0.0001$). Most patients receiving DM/Q (83.6%) exhibited a mean on-study decrease of at least three points in the CNS-LS compared

with 49.3% of placebo patients ($p < 0.0001$). Furthermore, those treated with DM/Q experienced approximately half as many inappropriate crying, laughing and mixed episodes. Secondary outcome measures, VAS scores for QoL and QoR also favoured treatment ($p \leq 0.0001$).

A treatment effect was noticed early and sustained throughout the study. On the basis of episode rates, DM/Q was statistically superior to placebo as early as the first week of treatment ($p = 0.036$). The proportion of patients with complete remission of emotional lability was significantly greater in the DM/Q group during every study period ($p \leq 0.04$).

Pain intensity scores were also evaluated as a secondary end point. Patients treated with DM/Q had an approximate two-fold greater decrease in pain intensity than those treated with placebo ($p = 0.0271$). Reported pain decreased by ~ 29% from baseline. These effects seem robust, particularly because this study was not powered for pain, and patients were allowed to use concomitant pain medications. These preliminary findings suggest that DM may be used to alleviate pain. Similar, ongoing studies are discussed in Section 9.

5.8.6 Correlation between improved CNS-LS scores and increased dextromethorphan levels

Notably, a correlation was found between the drug concentrations in plasma and the treatment effect in the MS trial. To establish this, plasma samples were taken from patients within 12 h of dosing. This analysis used all phenotypes and both treatment groups combined, and found a significant negative correlation between CNS-LS score and DM concentration in plasma on both day 29 ($n = 119$; correlation coefficient = -0.5041 ; $p < 0.0001$) and day 85 ($n = 90$; correlation coefficient = -0.4169 ; $p < 0.0001$). Thus, decreases in CNS-LS scores were correlated with increased plasma levels of the active ingredient in the combination therapy.

6. Safety and tolerability

DM/Q is generally well tolerated, with mostly mild or moderate AEs. Fortunately, most untoward side effects occur early. If patients do not tolerate DM/Q after taking it for a short time, it should be discontinued.

A combination product containing quinidine raises concern about an unintended effect on cardiac function, particularly the occurrence of a fatal arrhythmia. This is of special concern for patients with known QT prolongation, as quinidine and a number of other medications can lead to a torsade de pointes-based arrhythmia leading to ventricular tachycardia [78]. Although slight prolongation of the QT interval has been demonstrated in the ALS and MS trials, the changes are not thought to be of clinical significance. This is not surprising, considering that the dose of quinidine employed in the combination product is far below that employed for the treatment of atrial fibrillation [20]. In a

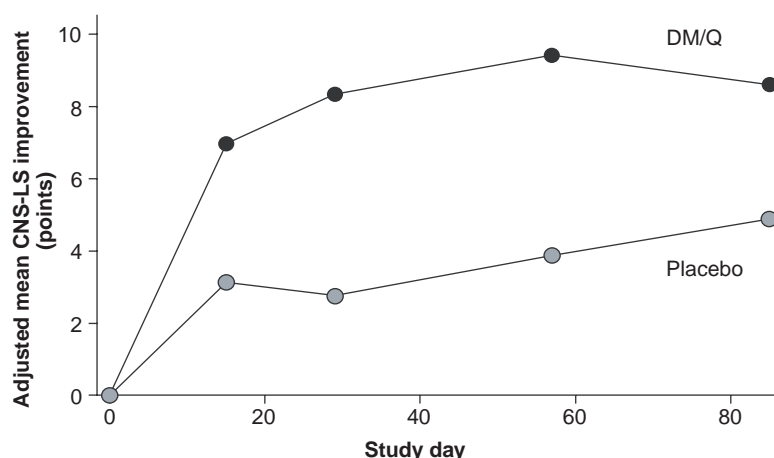


Figure 7. Improvement in CNS-LS score by study day observed in the emotional lability multiple sclerosis efficacy trial. Values shown are least-square means, adjusted for baseline levels and centre effects. At each time point, DM/Q patients exhibited a greater decrease in CNS-LS score compared with the placebo group ($p < 0.0001$).

Information from [77].

CNS-LS: Center for Neurologic Study-Lability Scale; DM/Q: Dextromethorphan/quinidine.

clinical setting of emotional lability, quinidine is unlikely to be detected in the serum of patients treated with DM/Q at the recommended dose [2].

In the ALS trial, a greater percentage of patients (24%) discontinued due to AEs in the DM/Q group compared with the DM and quinidine groups. However, in the MS study, there was little difference between the DM/Q and placebo groups (14.5 versus 10.8%, respectively). Significant differences between ALS treatment groups in the number of subjects experiencing an AE were observed for nausea, dizziness and somnolence, all of which are established side effects of DM. As quinidine enhances the bioavailability of DM, one would expect the incidence of DM-related AEs to increase with DM/Q. The only symptom that was more pronounced in DM/Q-treated MS patients was dizziness. Most instances were mild or moderate; only one patient reported severe dizziness. The median duration of dizziness was 1.0 day in DM/Q patients and 0.5 days in placebo patients. The median duration of nausea in the MS trial was 1.5 days in DM/Q patients and 1.0 day in placebo patients.

Interestingly, headache was the most common AE reported in the MS trial and occurred in more placebo patients than DM/Q patients, although the difference was not significant. Of further note is the finding that fatigue, a common MS-related problem, was not aggravated in the MS patients treated with DM/Q. The percentage of patients reporting fatigue was 19.7% in the DM/Q group and 20.3% in the placebo group, with a median duration of 1.5 days in DM/Q patients and 3.0 days in placebo patients.

For both the MS and ALS trials, no significant changes were observed in haematology, clinical chemistry or urinalysis in any treatment group. Electrocardiographic

findings were similar in the two trials. The results for the MS trial are likely to be more informative, as the trial was longer (3 versus 1 month). No significant difference between treatment groups was noted for the ECG parameters: QT or PR intervals, heart rate or QRS complex. The DM/Q group had a significantly greater change from screening to day 85 than the placebo group in QTc. The mean increase in QTc was small (7.5 ms in the DM/Q group versus 0.3 ms in the placebo group; $p = 0.0236$). No patient in either treatment group had an increase in QTc > 59 ms from screening to either follow-up visit, or a QTc > 500 ms at either follow-up visit.

7. Indications, dosage and administration of dextromethorphan/quinidine for emotional lability

If approved by the FDA, first-line use of DM/Q is recommended for the treatment of IEED secondary to neurological disease or injury (Avanir Pharmaceuticals: NEURODEX™ [dextromethorphan hydrobromide and quinidine sulfate capsules] proposed prescribing information to be submitted to the FDA. Avanir Pharmaceuticals, San Diego CA, USA 2006). DM/Q therapy (DM 30 mg plus quinidine 30 mg) is to be administered orally, twice daily (approximately every 12 h), with or without food. Administered at this dose, drug-related AEs are mostly mild or moderate. As it is likely that DM/Q will be administered chronically, it is important to note that its safety is supported by results from the ongoing open-label study in which patients have been treated for at least 6 – 12 months.

8. Regulatory affairs

A New Drug Application (NDA) and proposed labelling for DM/Q for the treatment of IEED was filed with the FDA in 2006. DM/Q holds the promise of becoming the first, proven effective therapy for IEED, also referred to as emotional lability or pseudobulbar affect.

9. Studies in progress: dextromethorphan/quinidine for the treatment of neuropathic pain

DM has been evaluated for the treatment of a variety of painful disorders, including the pain associated with peripheral neuropathy [79] and postherpetic neuralgia [80]. The results have been mixed, most likely because of the degradation of DM resulting from first-pass metabolism. Although the data are limited, DM/Q has been evaluated for the treatment of pain that occurs in two disorders: MS [77] and diabetic neuropathy (DN) [81]. The early findings with regard to improvement of pain in MS are discussed above, as part of the secondary end points in the MS trial (Section 5.8.5). The focus here is on DN.

9.1 Diabetic neuropathy: prevalence and mechanisms

DN is a common complication of diabetes and increases in prevalence with disease duration. At initial diagnosis of diabetes, 8% of patients have peripheral neuropathy; after 25 years with diabetes, 50% of patients suffer from the condition. About a third of the ~ 1 million individuals in the US who have symptomatic DN experience pain [82]. Along with pain, patients experience sensory loss and weakness, but pain usually predates the weakness. Patient descriptions of the pain include: burning, stabbing, a feeling of pins and needles, a toothache-like quality and so on. A lack of sensation is also disconcerting; patients report their feet feeling like wood or as if they are walking on cushions.

The pain of peripheral neuropathy results from both peripheral and central mechanisms [83]. In the periphery it is thought that spontaneous discharges in nociceptive fibres result from dysregulation of sodium channels [83,84]. Clinically, sodium channel antagonists, such as carbamazepine, mexiletine and lidocaine, have long been used to treat neuropathic pain [85]. Central sensitisation may involve a cascade of events, starting with repetitive firing of C fibres, which ultimately leads to activation of protein kinase C and phosphorylation of NMDA receptors decorating neurons in the dorsal horn [86]. This leads to increased excitability of this ligand-gated cation channel and, hence, central sensitisation.

9.2 Peripheral neuropathic pain: from mechanisms to symptoms

For this reason, NMDA antagonists have been investigated for the treatment of hypersensitive pain states, and have shown some promise in clinical trials, despite negative AE

profiles [87]. A second mechanism is represented by the failure of central inhibition, which is mediated principally by GABA and secondarily by other neurotransmitters such as monoamines and opioids [84,88]. Other mechanisms underlying the pathophysiology of neuropathic pain may involve topographic reorganisation within nerves and the spinal cord [83].

9.3 Open-label safety trial of dextromethorphan/quinidine in diabetic neuropathy

Given its NMDA antagonist properties, an open-label trial was conducted to determine if DM/Q would be tolerated in patients with painful DN, and to obtain insight into the dose that might be needed to exert a favourable treatment effect [81]. A total of 36 patients with DN were studied at five centres for 1 month. Following a 1- to 2-week discontinuation of analgesics, patients who experienced moderate-to-severe pain were treated with escalating doses of DM/Q, commencing with a daily dose of DM 30 mg/quinidine 30 mg. The response to therapy was monitored serially with standard pain scales (e.g., a pain intensity rating scale), and a standard QoL instrument was administered at the beginning and end of the trial.

Most patients tolerated the highest dose (DM 60 mg/quinidine 60 mg, every 12 h). As in earlier studies, the most common AEs were nausea (28% subjects) and dizziness (25%). Headache was also noted in 25% of patients. However, only two patients discontinued the trial due to AEs. The results, although promising, suffer from the inherent limitations of open-label trials. An ongoing double-blind, placebo-controlled study is scheduled for completion in 2006.

10. Expert opinion and conclusion

After decades of having been available on the OTC market as an antitussive agent, DM has been reintroduced as the active ingredient in the combination product DM/Q. Quinidine serves to increase the bioavailability and potential therapeutic utility of DM for diverse applications [3].

DM/Q has been shown to treat emotional lability secondary to ALS [70] and MS [77] in two Phase III clinical trials. If approved, patients with IEED suffering from a variety of neurological disorders could meaningfully benefit from treatment with DM/Q. Importantly, the positive efficacy findings in two diverse patient populations support the idea that there is a common anatomical substrate underlying loss of emotional control associated with neurological illness [44,48]. It follows that emotional lability should improve with treatment, irrespective of the primary neurological condition with which it is associated: Alzheimer's disease, stroke, traumatic brain injury, ALS, MS and Parkinson's disease [35,39]. An open-label trial of DM/Q is in progress to assess the safety of chronic treatment in patients with various neurological conditions, and may help to buttress this conclusion.

Phase III clinical data suggests that DM/Q can notably reduce or eliminate episodes of crying/laughing and that positive effects of treatment may be seen as early as the first week [77]. Outbursts of anger, frustration and impatience may also diminish in some patients [73]. Potential AEs, and those most commonly noted in clinical trials, include mild-to-moderate nausea, gastrointestinal complaints, dizziness and somnolence [70,77]. With continued use, some of these symptoms may subside. Most patients require long-term treatment [30], although in a minority of cases emotional lability may gradually resolve [31,89].

At present, many patients with emotional lability, some with even severe behavioural problems, remain inadequately treated; thus, the need for new therapeutic options [35,36]. DM/Q may be the first agent approved for the treatment of emotional lability. Off-label use of antidepressants has yielded only partial success [46], and may be limited by treatment-related AEs [47], particularly in the elderly. Importantly, clinicians need to recognise that emotional

lability is a distinct disorder, and is not to be equated with depression [44,65]. DM/Q provides a distinct and unique therapeutic mechanism of action. DM may exert a specific action on brain regions [1,27] implicated in emotional expression [49,50]. Thus, DM/Q offers a novel and potentially more selective approach for this unmet need in the treatment of emotional lability [36].

Acknowledgements

The author thanks the many patients who participated in the clinical studies and the colleagues who were involved in planning, executing and analysing them: S Appel, R Arnold, J Berg, B Brooks, U Calef, R Kaye, J Licht, L Pope and R Thisted. This work was supported individually by S and C Donnelly, M McKenzie and B Witt, and corporately by the Murry Sandler ALS fund, the Thagard Foundation, the William Stephen Trust and ultimately by Avanir Pharmaceuticals who had the vision to develop the product.

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Patents

101. SCHNIDER O, GRUSSNER A: US2676177 (1954)

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